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FIRST ANNUAL REPORT

OF THE

DIRECTOR

OF THE

New York State Pathological Laboratory

OF THE

UNIVERSITY OF BUFFALO.

TRANSMITTED TO THE LEGISLATURE JANUARY 26, 1899.

WYNKOOP HALLENBECK CRAWFORD CO.,
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STATE OF NEW YORK.

No. 32.

IN ASSEMBLY,

JANUARY 26, 1899.

FIRST ANNUAL REPORT

OF THE

DIRECTOR

OF THE

New York State Pathological Laboratory of the University of Buffalo

For the Year 1898.

Respectfully submitted to the Legislature of the State of New York, by

ROSWELL PARK,

Director.

REPORT.

The following report of the expenses and operations of the State Pathological Laboratory, located at present in and operated under the auspices of the Medical Department of the University of Buffalo, is herewith respectfully submitted. This laboratory was organized under the provisions of an item contained in the supply bill of the last Legislature, appropriating $10,000 for the purpose of "equipping and maintaining a laboratory to be devoted to the study of the causes, mortality rate and treatment of cancer," said money being appropriated to the Medical Department of the University of Buffalo. So soon as this appropriation became available the faculty of said medical department appointed me director of the laboratory and authorized me to proceed at once with its organization, offering it such accommodations as might be needed for its work within the building occupied by the medical school. Immediately complying with this authority, I first secured the services of Dr. H. R. Gaylord, an expert in pathology, well known on both sides of the ocean, and arranged with him to take charge of the work in pathology and temporarily in that of bateriology. The finest instruments known to science were ordered from different makers at home and abroad, a collection of books bearing upon the subject was begun and the rooms offered us by the University were furnished in such manner as to permit of carrying on the work. Later, about November 1st, Dr. H. D. Pease, formerly in the laboratory of the health department in the city

of Philadelphia, was added to the staff and placed in charge of the bacteriological work. There is no man in the country more competent to pursue this work than is he. As assistants in the prosecution of the study, Drs. F. C. Busch and N. W. Wilson have been engaged part or all of the time. A stenographer, an assistant and a janitor comprise, along with the director, the entire working staff. The salaries for this work during this time until February 1, 1899, amount to $4,238.33; the equipment of the laboratory, including all that has been spent for apparatus of all kinds, books, etc., has cost, up to February 1, $2,630.87; the current expenses during this time amount to $1,503.58.

Thus, up to February 1, 1899, the entire cost of conducting this laboratory has been $8,372.83. The expenditures, as itemized, are tabulated as follows:

	Salaries.	Equipment.	Stock and current expenses.	Total.
May — June	$480 49	$289 63	$443 34	$1,213 46
July	383 66	237 89	59 17	680 72
August	430 32	859 98	83 25	1,373 55
September	430 32	415 45	81 56	927 33
October	430 32	3 00	217 57	650 89
November	733 31	290 39	184 86	1,208 56
December	684 98	409 19	214 80	1,308 97
January	664 98	125 34	219 03	1,009 35
Total	$4,238 38	$2,630 87	$1,503 58	$8,372 83

Under stock are included such chemicals and supplies as are best purchased in bulk and which must necessarily be kept on hand, but which are constantly drawn upon and which will be ultimately exhausted and require renewal.

Under current expenses are included such supplies as must be purchased from day to day, as animal food, animals, meat, etc.

Permament equipment includes all apparatus and instruments which are only subject to possible injury and general deterioration, furniture, etc.

NEW YORK STATE PATHOLOGICAL LABORATORY

OF THE

UNIVERSITY OF BUFFALO.

ROSWELL PARK M. D., Director. H. R. GAYLORD, M. D., Associate.

The medical department of the University of Buffalo have great pleasure in announcing that during the spring of 1898 the Legislature of the State of New York appropriated a sum of money to this department for the purpose of " equipping and maintaining a laboratory to be devoted to the study of the causes, mortality-rate and treatment of cancer." This laboratory is now being conducted under the supervision of this department. Its existence is amply justified by the difficulty of the problems involved, the evidently increasing death rate from this disease, and the impossibility of studying it successfully by purely private means. The laboratory is equipped with every possible facility for investigating the disease, both in its clinical and pathological aspects.

The officers of the institution invite correspondence with physicians throughout the country in regard to statistics and all matters connected with this study; they also desire to secure reprints of all monographs pertaining to this subject for its library. They furthermore particularly wish to learn the names, addresses and, so far as possible, the methods in use, of the various quacks, charlatans and institutions advertising as curing this disease. Such correspondence will be regarded as absolutely confidential, if so requested.

It is desired also to secure specimens of tumors from all varieties of the lower animals, either gross specimens or fragments for microscopical examination. These should be sent securely packed, the former immersed in weak alcohol or formaline solution, the

latter in pure alcohol, and will be gratefully acknowledged, or even paid for in exceptional instances.

The coöperation of the entire profession is urgently solicited in this study, in order that it may be made more thorough and more complete.

During the summer of 1898 some 18,000 circulars, one of which is printed above, were distributed generally among the profession, mainly of this State. In this way, as well as through many of the medical journals, physicians throughout the State were invited to send specimens to us for examination and diagnosis. This is in order that diagnosis may be made much earlier than it often is, that patients may be given the benefit of the same, and is all in the direction of earlier recognition of this disease, if possible at a time when there is still a remedy for it in sight. Just in proportion as we can extend our sphere of usefulness in this way one of the most important functions and objects of the laboratory will be achieved. There is no reason why thousands of examinations of this kind may not be made if the physicians of the State would avail themselves of the opportunities here offered. This is, moreover, intended especially for those who are unable to afford such examinations when paid for at usual rates. It is intended, in other words, to institute a system here similar to that which prevails in various public laboratories in the great cities where examinations are made free of charge for diptheria, tuberculosis, etc. We seem to be on the point of being able to prove that cancer is a parasitic, possibly even an infectious disease. For reasons, then, of public safety, studying the welfare of the greatest number, it is of the greatest humanitarian as well as economic importance that somewhere such examinations of suspected cancer specimens can be accurately and reliably made. What may

be done in this direction is, perhaps, fairly exemplified in the laboratory of Prof. Orth, in Gottingen, where in twenty years some 2,300 specimens from suspected cancer of the uterus have been examined, with error in diagnosis in only three instances. What this all means to a given patient may be easily left to the imagination. The effect of this work, the value of the training which its performance gives to those engaged in the work and the extraordinary competency which is thus acquired might well be elaborated upon.

In the following tables it will be seen that there is a relative decrease in the mortality rate of consumption, which has steadily declined since the discovery of the peculiar germ to which it is due, a discovery made in 1881. Since the cause of this scourge of humanity has been known, intelligent and properly directed efforts have been able to very markedly decrease its ravages. On the other hand, the death rate from cancer is steadily increasing, not alone in New York State, but apparently in all parts of the world. This increase will undoubtedly continue until its minute causes are much better known, or positively determined. At present the research work of this laboratory is directed particularly toward this determination, and the work done even during the past few months would seem to indicate that we are laboring in the right direction. It is too early to make any detailed or scientific report beyond the general statement that already we have repeatedly succeeded in reproducing the disease in animals by inoculation from human patients, and are studying in the most earnest possible way the nature of the agent which can thus communicate it. Even though the rate of infant mortality has been reduced by modern sanitary measures, it appears from the tables

that more people die now of cancer at the so-called cancer age and fewer of old age than ever before.

Thus it can be plainly demonstrated that cancer is the only disease which is now positively and steadily upon the increase. There is need, moreover, for an entirely new department in this work. This comprehends the equipment of a laboratory in which investigations in physiological chemistry can be conducted for the purpose of examination of the blood, the secretions and fluids of the body, etc., in order to determine whether it may not be possible to recognize cancer of the internal organs before it begins to manifest itself by symptoms implying wide spread of the disease; in other words, at a time when there may still be an opportunity to saturate the system with some protective drug. The expense of equipment of such a department would be very small, a few hundred dollars sufficing. The salary of an expert would, however, be required, with, perhaps, that of an assistant. A series of most interesting and instructive investigations of this kind was carried on in Zurich, in 1895, by Moraczewski, but for only a short time and during a short time as incidental to other work. He has, however, abundantly shown what can be accomplished in this direction, and indicated a path to follow.

In time past there has been a lack of concerted action on the part of the profession in reporting and classifying tumors and in assigning deaths really due to them to their proper places. Undoubtedly, many deaths due to cancer have not been included under this head. An accurate statistical table would, therefore, necessitate extensive correspondence, which is out of the question. So necessary is proper and intelligent classification that the American Public Health Association at a recent meeting passed a resolution

binding itself to every effort toward this desired uniformity, offering to furnish blanks and instructions to physicians generally. When this is done, and deaths completely reported, the resultant figures will be found to be appalling. The American Surgical Association have also a special standing committee whose duty it is to study this subject and report annually upon the progress of their work. Thousands of deaths annually, doubtless due to cancer, are reported under that vague general heading "Deaths from other causes," the average general practitioner not being equipped with the apparatus by which accurate examinations of tumors, discharges, etc., can be made.

The progressive medical journals, both of this country and abroad, have since the establishment of this laboratory devoted much space to the general subject of cancer and cancer mortality. All agree that the question is a most serious one. An editorial in the New York Medical Record for November 5, 1898, stated that cancer was worse than consumption, that it is on the increase all over the world and that especially in this State it is startlingly increasing. In England and Wales, in 1840, there were 2,786 deaths from cancer, i. e., one to every 5,646 of the population, and one out of every 29 deaths. In 1896 there were 23,521 deaths from cancer, or one out of every 22 deaths, or, again, one to every 1,306 of the population. That is, the proportion of deaths to-day is nearly five times greater than it was fifty years ago. In the United States the increase is quite as alarming. The figures relating to New York State show a steady increase quite incompatible with the increase in population. In the comparison made below consumption has been chosen because it is perhaps the most widespread of all diseases, and the most generally dreaded, con-

sequently the most suitable for comparison. The figures used below are taken entirely from official sources, i. e., the reports and bulletins of the State Board of Health.

TABLE I.

(Monthly death rate from cancer in New York State for the past ten years).

This table illustrates how mortality from cancer has progressively increased.

	1887.	1888.	1889.	1890.	1891.	1892.	1893.	1894.	1895.	1896.	1898.
January	178	203	194	277	230	295	260	258	290	302	....
February	149	193	183	209	205	232	218	227	281	303	....
March	197	204	228	235	283	276	303	262	312	316	....
April	207	186	222	220	271	240	304	298	282	320	333
May	191	211	227	273	248	270	286	265	270	326	375
June	190	237	222	237	224	248	241	307	275	290	367
July	227	210	227	242	239	266	300	296	312	349	380
August	199	227	254	236	257	279	283	295	357	294	390
September	232	198	206	236	289	280	268	268	277	306	378
October	207	232	238	238	259	263	273	298	319	323	376
November	178	164	199	208	237	244	242	262	263	330	....
December	208	232	238	257	296	259	254	269	306	330	....

When, now, we compare cancer and consumption for the same years we find the increase standing as in

TABLE II.

(Comparison between cancer and consumption.)

	Cancer.	Consumption.
1887	2,363	11,609
1888	2,497	12,383
1889	2,638	12,390
1890	2,868	13,831
1891	3,028	13,445
1892	3,152	13,471
1893	3,232	13,123
1894	3,2[illegible]5	12,824
1895	3,554	13,267
1896	3,789	13,265
1898*	4,456	12,552

This table shows a constant and progressive increase in the cancer mortality year by year, while in the consumption column the mortality figures vary, those for 1898 being lower than for any of the previous eight years.

In the following table is shown the average monthly mortality of cancer and consumption for the past eleven years. Here, too, will be noticed a progressive and constant increase in the cancer column and a wide variance in figures in the consumption column.

TABLE III.

(Average of mortality by months from cancer and consumption.)

	Cancer.	Consumption.
1887	196.90	966.53
1888	208.00	1,031.75
1889	219.83	1,032.50
1890	239.00	1,152.58
1891	252.33	1,120.42
1892	262.66	1,122.60
1893	269.33	1,093.40
1894	275.41	1,068.66
1895	296.17	1,105 58
1896	315.75	1,105.41
*1898	371.28	1,071.00

*The average for 1898 is based on reports for seven months. These seven months' figures are the following:

TABLE IV.

(Monthly average death rate for 1898.)

	Cancer.	Consumption.
April	333	1,100
May	375	1,127
June	367	1,007
July	380	1,116
August	390	1,019
September	378	1,076
October	376	1,052

Comparing the monthly averages for the same months for the ten past years we find figures as given in

TABLE V.

	Cancer.	Consumption.
April	....	....
May	276	1,115
June	265	988
July	277	1,038
August	287	1,035
September	265	986
October	280	1,048

Studying now the figures as compared with population, the latter, as given in the ensuing table, are based upon the United States census reports for 1880 and 1890 and upon the State census for 1892. Increase of population is estimated at 100,000 per year from 1887 to 1890, and at 125,000 per year from 1890 to 1899. In this table the figures under cancer and consumption respectively indicate that one death from cancer or consumption has occurred in the number of the population printed. Thus, in 1887 one person in every 2,412 died of cancer and one of every 499 of consumption. The table also shows an increase of 40 per cent. in cancer during the eleven years tabulated. In other words, in 1887 one out of every 2,400 died of cancer, in 1898 one out of every 1,500. The same table shows that the mortality rate from consumption has exhibited a marked decrease.

TABLE VI.

Average of Deaths from Cancer and Consumption to the Total Number of the Population.

Year.	Population.	Cancer.	Consumption.
1887	5,700,000	2,412	499
1888	5,800,000	2,362	468
1889	5,900,000	2,239	476
1890	6,000,000	2,096	433
1891	6,125,000	2,022	455
1892	6,250,000	1,980	464
1893	6,375,000	1,972	486
1894	6,500,000	1,966	507
1895	6,625,000	1,862	499
1896	6,750,000	1,731	508
1898*	7,000,000	1,568	544

The population figures are shown in—

TABLE VII.

(Estimate of Population.)

1880	5,082,871	United States Census.
1890	5,997,853	United States Census.
1892	6,513,344	State Census.
1899	7,000,000	State Board of Health Estimate.

That this increase in cancer mortality is not due to improvements in methods of diagnosis is apparent. In fact, the reverse is nearer the truth, since many cases which were formerly diagnosed as cancer are now properly classified where they belong. Nor can the increase be explained by the assumption that the average age of the population has advanced, for in these days of specialism and progress modern life-saving is largely confined to the earlier years. The number of deaths of men under 35 and women over 45 has remained stationary. Deaths from old age have decreased, more people dying of cancer before they reach this age.

In none of the diseases tabulated by the State Board of Health, nor in any Government reports, has there been such an immense increase as in cancer. It is the only disease tabulated which shows a progressive and steady increase by weeks, months and years. Yet the world in general is ignorant of the awful array of these ever-increasing figures.

At the present rate at which this disease is increasing (and basing the estimate on figures for the past eleven years the averages are unchanged) it can be plainly seen that *ten years from now cancer will be claiming annually in New York State more victims than consumption, small-pox and typhoid fever combined.*

Contrast the above figures for this State with some others from other parts of the world. In 1889 there were 18,654 deaths from cancer in England, being 3.6 per cent. of the entire death rate for that year. In 1893 there were in London alone 3,412 deaths from this cause, making a percentage of 3.73 of the entire death rate. In Berlin, in 1892, there were 1,838 deaths from cancer, the rate being 3.48 per cent., while fifteen years previously it had been only 2.10, showing an increase of 1.38 per cent. in fifteen years. In Vienna the percentage of deaths from cancer in 1890 was 4.96, showing an increase of 0.84 in eight years. In Paris, in 1893, cancer caused 4.61 per cent. of the total deaths. Other cities in this country show increase as follows: Philadelphia, 0.26; Boston, 0.54; Baltimore, 0.65; New Orleans, 0.52; San Francisco, 0.84; all during the past ten years.

Showing how cancer is particularly prevalent in certain regions, we may take, for example, the recent report of Dr. Symons,

medical officer of Bath, England, who has found that in his territory cancer is 50 per cent. more frequent than in neighboring localities, and is increasing. There are also the extraordinary topographical and statistical studies of Behla, pertaining to the little town of Luckau, in Germany, where, within the past twenty-three years, there have been 73 deaths from cancer in an area covered by two or three city squares, as many as four deaths from cancer occurring in one house, where the disease has assumed the proportions and importance of an endemic. Similar endemic appearances of the disease have been noted in other parts of the world, and in mild form may be said to have almost prevailed in time past in certain localities in western New York.

These statements and statistics afford, it would seem, most convincing and unanswerable argument why the disease should be studied officially and at public expense. The problem as to the nature of cancer is the most important, and at the same time the most difficult of solution, of the many practical problems now before the medical profession. The causes of nearly all of the commonly known infectious diseases have been definitely established, and the value of the knowledge thus gained has been simply incalculable, since knowledge as to how to prevent them is now at hand, and their actual prevention depends rather on the enterprise and intelligence of the people generally. But this particular disease which kills thousands of people annually in this State, which affects seriously the domestic animals, and which, in another expression (for cancerous tumors destroy a large proportion of trees), is a serious economic disturbance, and which on this account might well

be studied by the Forestry Commission, has so far baffled the ingenuity and the ceaseless efforts of individuals for centuries. Surely had the problem been one capable of solution by individual effort it would have long ago been solved. As it is, however, it is necessary to study it from various directions, in an institution equipped with the best of talent and the most accurate instruments and apparatus, and from the side of the clinician, the pathologist, the bacteriologist and the chemist, as well as, perhaps, from the standpoint of the statistician, the geologist and the botanist. To illustrate the latter point first, a careful statistical study will show where the disease prevails in its most pronounced form, and it may be that the researches of the geologist and the botanist will show the nature of the soil which furnishes the drinking water, or the vegetables, cereals and fruit which, raw or cooked, furnish the vegetable food of the inhabitants. As indications point more and more strongly toward the parasitic nature of this disease, we must investigate the air, the drinking water, the food and the surroundings in order that the parasite, when discovered, may be avoided.

Coming now to the more purely medical side of this matter, it is the general practitioner who first comes in contact with these cases, and it is the general practitioner who is most often puzzled with regard to early diagnosis. It is first evident that if a successful remedy for cancer is ever to be evolved, it would be necessary to see it early, rather than late, in order to attain success. Early employment of such ideal remedy means early diagnosis, and this, at present, is a matter of the greatest difficulty. Every means, therefore, which can be placed at the dis-

posal of the medical profession by which early recognition can be facilitated is a step in the desired direction. If sufficient help in this direction be afforded it is intended to furnish to any physician in this State who desires it, directions for preparing and forwarding to this laboratory specimens of tumor, discharge or excretion for examination with regard to the possibility of cancer, and to do this free of charge in all desired cases. In this respect this State Laboratory would be much like the laboratories maintained by various city health departments, to which are sent cultures made from diphtheria, tuberculosis, etc., for examination. The co-operation and assistance of physicians throughout the State has been already invited by means of circulars similar to that already copied, of which some 18,000 were sent out during the past year. If the physicians of New York State will but help in this matter this Laboratory may be a means of doing great good in this direction, though it should accomplish nothing else, because nineteen out of twenty of the physicians are not equipped with the necessary apparatus and technical skill to do this work as it must be done to be accurate.

The problems before the bacteriologist and the pathologist in this investigation are most complex and perplexing. Already, however, in this laboratory, as in instances in other parts of the world, it has been possible to make numerous successful inoculations of cancer from man to animals. The nature, however, of that agent, whatever it may be, which thus can communicate the disease, is by no means definitely established, and has so far resisted the most painstaking study. It must necessarily be some living agent, however, and capable of cultivation upon something; and it is part of our work to discover the conditions which make

its growth possible and to study its life history. Only a certain amount of familiarity with the general difficulties attending this line of research can acquaint one with the peculiar difficulties surounding this particular problem. We hold it, however, to be established that cancer is both a communicable and a parasitic disease, and feel that with patience and scientific effort the nature of the communicable agent can some time in the future be determined.

The investigation and pursuit of this parasite, or these parasites (since probably there are several), must take the pathologist of this institution into hitherto unexplored and unfamiliar fields. The amount of time required in, as it were, chasing the different organisms through their life histories and peculiarities is to the uninitiated astonishing. But there are many side lights which must be shed upon the principal problem in which we are engaged. For this purpose, as already intimated, the clinicians must furnish the material, the pathologists must investigate it with the microscope and record their observations with photographic apparatus; the bacteriologists must study it with their culture methods, while the physiological chemists must have access to patients at all times in order to examine the blood, the urine and other fluids, and see what changes occur at various times and under various conditions. All of this means three different laboratories; namely, the pathological, the bacteriological and the chemical, whose chiefs are working in closest harmony with the clinician, who comes in daily contact with the patient.

With regard, now, to our actual needs and necessities for the future, these comprise, first of all, more space, and much more space if the work is to be properly carried on. The accommoda-

tions requisite for this purpose, especially if results obtained are to be demonstrated, call for a small building whose total expense should not exceed $25,000. With such a building, the finest research laboratory in the world could be properly housed and accommodated.

This building being provided could be maintained for the ensuing year at an expense probably not to exceed $15,000, including therein all legitimate expenses of any building, with salaries of chiefs and assistants, further equipment and the beginning of a collection of special works in various languages, bearing upon this subject. Consequently, we request your honorable body to afford us the means of carrying on the work above asked for, and for the specific purposes herein set forth, feeling that the intrinsic importance of the subject and the vital interests of citizens of the Empire State, justify any reasonable expense by which may be learned first the nature, and later the means of mitigating, if not curing, the most serious and perplexing disease now known to the medical world.

It may be proper to say that the investigations and results furnished from this laboratory have been, and shall hereafter be furnished from time to time to the high-class medical journals of this country and Europe, to be collected and published by the State if the Legislature deem best. The channel through which such information is usually furnished to the medical profession is that already adopted, as above, but there would be the best of reason for collecting and printing these papers in separate form by themselves. As illustrative of work already done in this laboratory and in this direction, I would mention a paper on "Syncytial Tumors," by Dr. H. R. Gaylord, published in the American Journal of Ob-

stetrics, Vol. 38, No. 2, 1898, and a paper on the "Etiology of Cancer," published by the director in the American Journal of the Medical Sciences for May, 1898, copies of which are to be had on application.

I have hardly thought it necessary to go into the minutiae of the scientific work of this laboratory, feeling that this was hardly the time at which to submit a technical scientific report. I can only say in closing that the most eminent scientific men of this country have already expressed themselves as deeply interested in its work, and hopeful of future results from its operation. I know not how to make a stronger appeal for continuance and augmentation of support than I have submitted in simple untechnical language in the foregoing statements. Summarizing them all, I will say in closing, that according to the census returns of the United States Government, western New York lies in an area, of which Buffalo is nearly the geographical centre, where the death rate from cancer is higher than in any other part of the country, and that, as I have shown by quotations from the State Board of Health returns, this rate is increasing not only in the western part of the State, but everywhere. Can there be any more eloquent argument or any fitter object for public aid than this which I have the honor to respectfully submit?

DANIEL LEWIS, M.D.
COMMISSIONER.

NEW YORK
STATE DEPARTMENT OF HEALTH
ALBANY

C. B. P.

December 1st, 1904.

Edwin H. Brigham, M. D.,

Boston Medical Library,

8 The Fenway, Boston, Mass.

Dear Sir:—

I am in receipt of your communication of the 30th ult. acknowledging receipt of a copy of the 4th Annual Report of the work of the Cancer Laboratory for the year 1902-3, and note your request for copies of all other reports that have been published, and to be placed on our mailing list for future issues.

other reports that have been published, and to be placed on our mailing list for future issues.

In reply you are informed that the Director of the Laboratory, Dr. Roswell Park, has been requested to send you copies of the 1st, 2nd and 3rd Reports covering the work of the Laboratory.

The Boston Medical Library has been placed on our mailing list.

Very respectfully,

Daniel Lewis,

Commissioner of Health.

By T. A. Stewart

Chief Clerk.

H. B.

SECOND ANNUAL REPORT

OF THE

NEW YORK STATE

Pathological Laboratory

OF THE

UNIVERSITY OF BUFFALO.

FOR THE YEAR 1899.

TRANSMITTED TO THE LEGISLATURE FEBRUARY 21, 1900.

ALBANY:
JAMES B. LYON, STATE PRINTER.
1900.

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TRANSMITTED TO THE LEGISLATURE FEBRUARY 21, 1900.

ALBANY:
JAMES B. LYON, STATE PRINTER.
1900.

STATE OF NEW YORK.

No. 28.

IN SENATE,

FEBRUARY 21, 1900.

SECOND ANNUAL REPORT

OF THE

New York State Pathological Laboratory of the University of Buffalo.

For the Year 1899.

STATE OF NEW YORK—EXECUTIVE CHAMBER,
ALBANY, *February* 21, 1900.

To the Legislature:

I have the honor to transmit herewith the Second Annual Report of the New York State Pathological Laboratory of the University of Buffalo, the same being for the year 1899.

THEODORE ROOSEVELT.

REPORT.

This Second Annual Report of the New York State Pathological Laboratory of the University of Buffalo is herewith respectfully submitted. It covers the second year of its existence and includes the period from February 1, 1899, to February 1, 1900. Ever since the first appropriation of money for this purpose by the Legislature of the State of New York, work has been actively and painstakingly carried out in the direction for which the laboratory was organized and equipped. It is still occupying quarters in the building of the Medical Department of the University of Buffalo, and has an equipment for its pathological and bacteriological department which is liberal and ample for the purpose. There still remains to be equipped and commenced a third department, i. e., one for physiological chemistry, which is exceedingly important in the direction in which we are studying and from which large returns are expected in the knowledge to be gained from the study of the chemical problems presented by our investigations. The other special needs of the Laboratory, aside from expenses for conduct of the same, are in the direction of a good library, which shall contain the records of all the work done by others during the past few decades.

The organization of the Laboratory remains practically unchanged. Dr. H. R. Gaylord has been made the Director of Laboratory Work, and has for colleagues Drs. Herbert D. Pease and Irving P. Lyon, with a staff of assistants including three laboratory assistants and one stenographer. In addition to this staff special work has been done by Drs. N. W. Wilson and Lawrence

Hendee. A somewhat detailed account of the amount of work done duirng the past year will be found below. It is proposed with the further assistance of the Legislature to secure for the ensuing year the services of an expert chemist for the purpose above set forth.

Following is a table showing the cost of conducting this laboratory for the year beginning February 1, 1899, giving an epitomized and tabulated statement of expenditures:

Month.	Salaries.	Equipment.	Stock and current expenses.	Total.
February	$664 98	$26 62	$69 13	$760 73
March	664 98	53 45	58 94	777 37
April	598 32	....	80	678 32
May	598 32	....	20 00	618 32
June	621 65	464 31	225 60	1,311 56
July	654 99	15 00	103 05	773 04
August	654 99	104 15	104 26	863 40
September ...	704 99	80 00	70 52	855 51
October	729 99	27 05	1,096 64	1,853 68
November	763 33	219 72	155 85	1,138 90
December	713 33	266 42	316 46	1,296 21
January	713 33	662 81	225 41	1,601 55
Totals	$8,083 20	$1,919 53	$2,525 86	$12,528 59

During the year past Dr. Gaylord was authorized to go abroad to study the methods of investigation in the best laboratories of Europe, and to familiarize himself with work already accomplished or in progress. His traveling expenses are included in the above statement. The value of his trip to the laboratory was very great, since by personal acquaintance our workers were put in personal touch with the investigators of Europe, and a great deal of time which would otherwise have been wasted was

thereby saved. There is the same value to investigators in this work in dividing and organizing their efforts that is recognized among astronomers, who freely exchange notes between their respective observatories.

A great deal of interest has been aroused all over the world by the foundation of this, the first institution for the study of cancer. Scarcely a medical journal in Great Britain or in this country has failed to make note of its existence and to comment most favorably upon its purpose and the wisdom of its foundation. For instance, at the meeting of the American Public Health Association in Minneapolis, last fall, the following resolution was introduced and unanimously passed, and is quoted from the Journal of the American Medical Association for November 18, 1899, page 1291:

"Dr. A. Walter Suiter, Herkimer, N. Y., offered the following resolutions:

"Whereas, the encouragement of the endowment of research in the science of etiology and prevention of diseases is entirely within the province and mission of the American Public Health Association, and

"Whereas, by recent legislative action the State of New York has taken a decisive step in advance by the grant of an annual appropriation for the establishment and maintenance of a laboratory, with all modern appliances, for the persistent prosecution of studies in the etiology of cancer, and

"Whereas, results have already been obtained which lead to the hope that the discovery of the etiological factor in the production of this much dreaded disease may be at hand, therefore

"Resolved, That the American Public Health Association take this occasion to place on record its approval of all similar efforts,

to the end that state and national patronage in special and general scientific research may be universally established."

In the Philadelphia Medical Journal for October 28, 1899, on page 817, is the following quotation from a paper on cancer by Professor Rodman:

"The Empire State has, through an appropriation by its Legislature, located and equipped a pathological laboratory at Buffalo, the center of the cancer district, that the disease might be investigated in the most scientific manner at public expense. * * It cannot be questioned that other States, especially Pennsylvania, which has dealt with its charities in such a generous way, will soon follow the worthy example of New York and establish a laboratory for the better study of this pitiless enemy of civilization, which is increasing in such a startling way, and which to-day enjoys the melancholy distinction of being the only disease that has completely baffled and set at naught the work of sanitarians."

Take, again, the following from the Journal of the American Medical Association for October 21, 1899, page 1047:

"The value of collective investigation of carcinoma with the object of bringing out all kinds of reliable data, peculiar local conditions, etc., is quite apparent. So far, this country has been the only one in which there has been established a State Laboratory for the exclusive investigation of carcinoma and tumors in general. The great State of New York supports such a laboratory in Buffalo. * * * We need many such institutions scattered over the United States, as well as in foreign countries, so that the great and unsolved problems of malignant tumors may be properly attacked."

In an editorial in the London Lancet for August 26, 1899, page 580, occurs the following:

"There is, however, one aspect of the question which will, we are confident, be as gratifying to our correspondent as it is to ourselves, viz., that both in the United States and in Great Britain scientific workers are already at work for the investigation of the nature and causes of this terrible malady, and we shall both concur in hoping that effective means may eventually be discovered of checking its progress, a feat that has already been accomplished in the case of that not less dreadful complaint, pulmonary tuberculosis."

The general interest shown in this field of investigation all over the world is also illustrated by the following paragraph from an editorial in the British Medical Journal for July 1, 1899, page 36:

"As is shown by several papers published in our columns within the last few months, investigations are being made by many skilled observers who are working along different paths toward a common object—the elucidation of the etiology of cancer. This question is surrounded with the most serious difficulties; but there appears to be a reasonable hope that the mystery in which the origin of the most dreaded of all diseases is still enshrouded may before long be dissipated. A field of inquiry which seems likely to be fruitful of important results is the local distribution of cancer, which, as has been shown, haunts particular regions, and even, it is thought by some, particular houses."

The foundation of this laboratory by New York State excited an interest in London which took form and shape in the organization of a formal society for the study of cancer, which has already assumed large proportions and an important position. In the

meeting which was called for its organization the purposes and character of this laboratory were set forth at length and held up as a model for imitation and reason for organization. The outcome of its foundation was a formal interrogation in the House of Commons by Sir Charles Cameron, the president of the Cancer Society. The outcome of this interrogation was the following correspondence, which is quoted verbatim:

DEPARTMENT OF STATE,
WASHINGTON, *July* 25, 1899.

His Excellency the Governor of New York, Albany, N. Y.:

Sir.—I have the honor to enclose for your information copy of a note from the British Embassy at this capital, asking the Department to procure for it copies of any official reports which may be obtainable on the subject of a laboratory at Buffalo, said to be endowed by the Legislature of New York, for the study of cancer.

You will observe that the request of the Embassy is based on a question asked in the House of Commons by Sir Charles Cameron, calling attention to the institution in question.

I have the honor to be, sir,
Your obedient servant,
(Signed) JOHN HAY.

Enclosure from Mr. Tower, July 20, 1899.

WASHINGTON, 20th *July*, 1899.

Sir.—By direction of the Marquis of Salisbury I have the honor to request you to be good enough to procure for me copies of any official reports on the subject of a laboratory at Buffalo, endowed by the Legislature of the State of New York, for the study of cancer.

The present request is based on a question asked in the House of Commons by Sir Charles Cameron, who called attention to the institution in question.

I have the honor to be with the highest consideration,

Sir, Your most obedient humble servant,

(Signed) REGINALD TOWER.

STATE OF NEW YORK—EXECUTIVE CHAMBER,

ALBANY, *July* 27, 1899.

To the Secretary of the Medical Department of the University of Buffalo, Buffalo, N. Y.:

Dear Sir.—I am directed by Governor Roosevelt to forward you the enclosed communication from the Secretary of State at Washington, which explains itself, and to request that if possible you furnish this office with the information desired. Will you kindly return the enclosures?

Respectfully,

WM. J. YOUNGS,

Secretary to the Governor.

In consequence of this correspondence there was forwarded through the proper channels the information which was desired.

The London Cancer Society also sent an accredited representative to this country, especially to this laboratory, last fall, in the person of Dr. Arthur C. Duffey, who came with a formal letter of introduction from its president. Dr. Duffey remained here for several weeks studying our methods and results, but has as yet made no formal report to which I can refer.

Last year a goodly portion of the first annual report of this laboratory dealt with figures in tabulated form. The inevitable conclusion to be drawn from them was that cancer as a disease is alarmingly on the increase. These conclusions were challenged

by a few, not disinterested, students of the subject. However, no sufficient reason has yet been advanced for changing them. On the contrary, such statements as these quoted below taken from absolutely reliable and reputable yet disinterested sources can but serve to strengthen them.

Thus, for example, the London Lancet in an editorial (May 20, 1899, p. 1376), says:

"Next in importance to tuberculosis in the list of constitutional diseases stands cancer, which, on account of its rapidly increasing fatality in recent years, has awakened an amount of general interest scarcely less than that which rightly attaches to the still excessive prevalence of tuberculous disease. The national records tell us that for some years past cancer has contributed more largely to the death-roll than any other single disease, with the exception of bronchitis, pulmonary consumption and pneumonia. * * * The earliest accessible records of mortality are those relating to the years 1851-60. In that decade cancer was fatal, on the average, to 317 persons annually out of each 1,000,000 of the population. The table shows that during this period cancer claimed more than twice as many victims among females as it did among males, and ever since that period the disease has shown a similar tendency, although the contrast has been less strongly marked. It will therefore be expedient to consider separately the mortality of the two sexes. Taking the five groups of years consecutively, we note that cancer mortality among males was equal to 195 per 1,000,000 living in the first period, 242 in the second, 312 in the third, 430 in the fourth, and 571 in the last period. Among females the rates per 1,000,000 were 434, 519, 617, 739 and 882 respectively; thus the mortality in both sexes showed a marked and progres-

sive increase from period to period. If, therefore, the correctness of the rates be assumed without question, it would appear that within rather less than half a century the fatality of malignant disease in both sexes has at least doubled. There are good grounds, however, for the belief that the increase shown by the tables is not wholly real. * * * Nevertheless, after making every possible allowance it would appear to be unsafe to compute the cancer mortality in the seven years 1891-97 at less than 551 per 1,000,000 for males and 863 per 1,000,000 for females. These rates correspond to an average annual increase of 2.9 per cent. and 1.8 per cent. respectively, as compared with the mortality in 1861-70."

In the University Medical Magazine for November, 1899, p. 110, we find the following:

"Cancer and tubercle are, beyond doubt, two of the most important subjects before the profession to-day. The former occurs with alarming frequency, and is steadily on the increase; the latter carries off one-seventh of our total population. Both have so far absolutely resisted all attempts that have been made to effect a cure.

* * * * * * * * * * * * * * * *

"A table showing the death rate from cancer in England for each decade since 1851 shows an increase in the last or fourth period of 86 per cent. for all ages, and of over 100 per cent. after the 55th year of life. In Scotland the mortality rate for carcinoma has steadily risen from 404 per 1,000,000 living persons, in 1861, to 770 in 1897. It is higher in the eight large towns of Scotland than in the 'insular rural districts.' In Ireland the death-rate is lower than in either England or Scotland. It shows an increase, however, from 370 in 1881 to 580 in 1897. In Nor-

way the rate in 1877 was 320, and in 1887 it was 600. In Prussia it was 310 in 1881 and 380 in 1887. In New York city the returns show a rise from 400 in 1875 to 530 in 1885. In New Zealand a steady increase has been noted since 1881.

"The first criticism that would suggest itself in considering these figures is that the difference may be explained by more accurate diagnosis, and by greater care in registration in recent years.

"In reply to the first of these, Dr. Payne very justly says that there has not been any revolutionary advance in the matter of diagnosis of carcinoma and of sarcoma, for his figures include both; and while there is doubtless greater discrimination in the matter of registration in recent years, all authorities agree that this cannot explain the very great difference in the figures. In order that this source of error might be excluded as largely as possible, the present inquiry begins with the year 1851, before which the records were less reliable than since that time."

In the Contemporary Review for July, 1899, p. 105, is an article on the Cancer Problem, by Hutchinson, who says:

"And as the deaths per thousand living from this malady have almost doubled in England, and nearly trebled in the United States, during the last 30 years, if official statistics are to be taken at their face value, the contrast is a sufficiently striking one. To find that, in spite of our utmost endeavors, cancer has apparently doubled the number of its victims in the very same period that even the widespread and intractable 'white plague of the North,' consumption, has been baulked of more than a third of its yearly death-tribute, is enough to give the most heedless of us a pause. What wonder that the conviction is rapidly crystallizing in the medical mind that, since the tuberculosis

question has been set in a fair way towards solution, the coming problem, the riddle of the Sphinx for the Twentieth century, is that of cancer? To a twelfth of us who have passed the age of 40 it is indeed a riddle of the Sphinx, for unless we solve it it will destroy us."

Even since the preparation of this report was begun there has appeared striking corroboration of all that has been stated, so far at least as American cities are concerned. In the American Journal of the Medical Sciences for February, 1900, p. 170, is a paper by Dr. Massey, of Philadelphia, entitled, "The Increasing Prevalence of Cancer as Shown in the Mortality Statistics of American Cities." This paper is illustrated by graphic charts illustrating the ratios of cancer deaths per 100,000 living population, and more than justifies the ground taken above.

A most cogent plea for collective investigation of cancer has been recently published by Katz, of Hamburg (Deutche Med. Woch., 1899, Nos. 16, 17). He calls attention to the unsatisfactory explanation afforded by many of the theories now in vogue, and argues logically and convincingly in favor of the method by concerted investigation, and particularly the statistical method. It was Mars d'Espine who perhaps set us our first example in the direction of statistical study, when he reported the statistics for 13 years in the Canton of Geneva, a careful study which has not yet found a sufficient number of imitators. The special interest of Katz's paper for us, at present, is the corroboration which his own studies afford of the statement so frequently made that there is every reason to think that cancer, as a disease, is upon the increase. Katz shows, for instance, from a study of Hamburg conditions, the experience of private practice and the mortuary as well as pathological statistics of the Gen-

eral Hospital there, as well as by the studies of E. Fraenkel, that in that city, for instance, there is a well-marked increase in the percentage of cancer. Moreover, this statement is accentuated by statistics from all over the world, which seem to show that not only is the disease upon the increase, but that the age of liability is becoming younger, and that it is rather among the better classes of people than the lower in whom it seems to predominate. Katz concludes his paper by a recognition of the difficulty of collective investigation, and at the same time by a statement that it is of the greatest importance that it should be undertaken.

A topographical study of the disease will render great aid in solving some of its mysteries. As classical models for such studies we may refer to Powers' paper on "The Local Distribution of Cancer and Cancer Houses," in the April (1899) number of the Practitioner, the studies contained in the British Medical Journal before July 1, 1899, with the editorial comments thereon, and the paper by Lloyd Jones on "The Topographical Distribution of Cancer," in the British Medical Journal for April 1, 1899.

What could be more accurate, in such work, than Jones' method, which he describes as follows:

"Having obtained a list of the houses in which persons had been taken ill with cancer, I proceeded to visit the houses and to mark each one on an ordnance map—scale of 10 feet to a mile—showing the affected and the non-affected houses in red and black respectively. This map of the borough showed at once that certain districts were fairly free from cancer, while other regions were far more extensively affected. The areas most affected of all showed 1 case in every 2 to 5 houses; the most healthy areas,

from this point of view, showed only one case (or no case) in every 60 houses."

The figures obtained were as follows:

Total number of houses concerned....................	5,685
Unaffected houses	5,247
Affected houses	438

Showing a mean of 1 affected house to every 11.9 unaffected houses. Multiple cases in the same house divisible into:

(1) Double cases, 7.

(2) Triple cases, 3.

But as showing what can be accomplished in our own rural districts in this same line of work, if only the necessary zeal and intelligence be applied to it, take the following illustration furnished by Dr. John E. Sutton, of Albion, Orleans county. He writes: "During the last five years or so there have occurred, from all causes, within a range of 1⅛ miles of a small hamlet near Albion, N. Y. (Rich's Corners), sixteen deaths. Of these nine were unquestionably from cancer; two were probably caused by cancer, judging from the history of the cases as learned from friends. Of the remaining five, one died of a pistol-shot wound, leaving four of the sixteen as dying of disease other than cancer. There are at present two other cases living in the territory mentioned."

Lloyd Jones, in his paper above referred to, has summarized the views of various observers so succinctly that a brief portion of it is reproduced here:

"Briefly the following are the points upon which, in each case, several of the most trustworthy authors are agreed:

1. That cancer picks out certain districts, and that there are areas of immunity and cancerous areas (Shattock, Noel, Guelliot, Behla).

2. That immune areas may lie close beside cancerous areas (Pfeiffer, Noel).

3. That malignant disease is most common along the banks of rivers or streams (Pfeiffer, Haviland, Fiessinger, Noel, Nason, Blake).

4. That elevated districts or plateaus are more free from cancer, while low-lying districts carry more liability to its inroads (Pfeiffer, Noel, Haviland, Fiessinger, Nason).

5. That isolated "cancer houses" or groups of such houses occur in certain districts (Pfeiffer, Fiessinger, D'Arcy Power, Scott, Chapman, Noel, Ogle, Guelliot).

6. That cancer houses often occur near to woods (Fiessinger, Noel), orchards (Fiessinger) or forests of firs (Noel).

7. That persons living upon flooded and clay districts and retentive soils are especially liable to its ravages (Haviland, Butlin).

8. That limestone districts are comparatively free from cancer (Haviland) but do not confer absolute immunity.

9. That cancer may be disseminated by means of water (Fiessinger, Noel, Haviland, etc.); that it depends upon the presence of decaying animal or vegetable matter or sewage (Haviland, Noel).

10. Lastly, the suggestion is thrown out by three observers that insects play a part in the dissemination of malignant disease (Morau, Fiessinger, Noel). Of these three the first is the only one who adduces anything like proof of his assertions."

The parasitic theory in explanation of cancer is that which is to-day most vehemently discussed. It is, however, far from new, for without going back to the views of ancient writers, Harvey (Exercitationes, 1651) wrote that tumors resemble strongly those perasitic productions which we see in the vegetable kingdom,

while John Hunter thought that cancer was caused by the presence of an entozoon, and Adams regarded an animal parasite as undoubtedly the cause of cancer. Of late, however, it has taken more particular form and shape, and is being tested by all the canons of modern scientific criticism. Enthusiasts, working under the inspiration of this theory, were easily tempted, however, to lose sight of the tumor side of the question while hunting for the parasite. However, it is not a question of any one parasite, nor at first whether these hypothetical parasites belong to the animal or to the vegetable kingdom. *The primary question is whether cancer is due to intrinsic or extrinsic causes.*

When the State of New York by appropriation established a laboratory for the investigation of cancer it devolved upon those who had charge of the work to elaborate a rational plan by which the subject could be properly approached. Necessarily, the first steps in such an investigation had to be taken along conventional lines, and so extensive and yet scattered has been the work of various investigators of the subject that it has required a considerable period of time and no small amount of effort to thoroughly collect and classify the material at hand. It was decided in the beginning that the subject must be as much as possible approached from all sides, but the limitations of our appropriation have thus far rendered it only possible to carry out an elaborate pathological and bacteriological research. From the beginning the plan has been to add to these two sides of the question a complete and full investigation along chemical lines. Aside from the fact that our present quarters and appropriation have thus far not permitted our undertaking this third branch, the proper man was not apparent, and it is only within a short time that such a scientist has been obtainable. In making to you a short report of the amount of

work which has been accomplished, I wish to particularly emphasize that much of the work which may at first glance not appear of great importance has been none the less necessary, and has required as great care and protection as work which we are at present conducting and which gives promise of much that is positive. Pathological investigation has consisted in histological examination of tumors hardened by all of the approved and modern methods, stained after various formulae of different investigators and scrutinized with great care for parasites. Various attempts to harden and stain these bodies had met with only partial success when we came into possession of an article published by H. G. Plimmer, in the Cancer Number of the Practitioner. Plimmer investigated during a period of six years over 1,100 carcinomata, and, by a special staining method, has succeeded in demonstrating the presence in practically all carcinomata of certain characteristic bodies which we are now able to say are identical with those which had been observed by Dr. Gaylord in the fresh state. Since employing Plimmer's method Dr. Gaylord has been able to demonstrate in all carcinomata examined the characteristic appearances described by Plimmer. In many cases these bodies are very few in number and only prolonged search will disclose them. Plimmer reports some success in the cultivation of these organisms, and although we have as yet been unable to obtain the organisms by culture we are at present working upon an indirect method by which we hope we shall ultimately succeed in isolating the organisms in all cases where present.

To indicate the fruitlessness of ordinary bacteriological research along old and classical lines, it will suffice to give a short résumé of the large number of cultures which have been made in the State Laboratory from various tumors, and the results which

these investigations show: Number of cultures studied from tumor cases, 1,226. (This does not include probably as many more, not recorded, but made and studied from cases ascertained later on not to be neoplasms, and cultures made and studied during the investigation of micro-organisms, especially yeasts and fungi not derived from tumors.)

Sixty different kinds of culture media were prepared and used in the investigation.

Number of animals inoculated:

(a) With fresh tumors	46
Number of these dead, 32.	
Average duration of life, 78 days.	
(b) With fluids from fresh tumors or from localities (peritoneum, etc.) containing tumors	22
Number of these dead, 22.	
Average duration of life, 73 days.	
(c) With cultures of micro-cocci or their products, obtained from tumors	21
(d) With tissues or fluids from animals previously inoculated, as above	4
(f) New work on animals with yeasts	15
Of which there are living, 9.	
Of which there are dead, 7.	
Total	118
Cases of tumors investigated histologically	175
Cases worked out completely, 76.	
Cases for diagnosis alone, 99.	
Sections cut, stained and examined, over	2,500
Blocks of tissue from animals, cut	216
Sections examined, over	1,200

In analyzing these figures it will be seen, first, that the inoculation of animals with fresh tumors (46 times) has in no case resulted in the transplantation of carcinoma from man to animal; the animals have, however, in each case perished after an average period of 78 days, showing symptoms of marked cachexia and with enlarged lymph nodes.

Our most recent work, by which we are introducing tumors into animals, employing another method, has resulted in the discovery of the fact that by the employment of proper staining methods the parasites found in cancer may be detected in large quantity in the enlarged lymph nodes of the experimental animal. This work is still in progress, and we are not prepared yet to publish it in full. In one case Dr. Gaylord succeeded in producing a true adenocarcinoma in an animal by inoculation with fluid from the peritoneal cavity of a man suffering from colloid cancer of the omentum. In this fluid was observed the presence of an organism which apparently belongs to the yeast group, but which we are unable to cultivate. The organism in the original fluid was injected into the jugular vein of a guinea pig and after three weeks and a half the animal was killed, whereupon minute nodes of beginning adenocarcinoma of the lung were found. This is the first positive case of this kind, and holds out to us the definite hope that when we are able to understand the nature of these organisms we may be able to produce carcinoma in animals with organisms obtained from carcinoma in man. The Laboratory is in possession of pathogenic yeasts with various investigators (Sanfelice, of Cagliari, and Plimmer, of London) have isolated from cancer, and we are now carrying on an elaborate investigation in the first steps of which we have been able to confirm all that Plimmer has published. The principal difficulty which we encounter at present is an entire lack of required knowledge on the part even of botanists of the nature

of the organism in question. These organisms are exceedingly polymorphic, and it requires prolonged experimentation to determine the relation between certain definite bodies found in the tissue, which are presumably these organisms, and the appearance of the same organism when grown upon artificial culture media. In this direction our recent experiments are rendering us great aid, and we have been able to confirm the identity of the bodies described by Plimmer and observed by ourselves in the fresh state, with the organisms which Plimmer has been able to cultivate. In his examination of 1,100 tumors Plimmer has been able only in five cases to obtain a culture of the organism upon artificial culture media, indicating that the cultivatability of the organism is exceedingly variable. Therefore, the large number of cases in which we have obtained negative results indicates nothing more than the fruitlessness of attempting to study organisms of unknown habitat by conventional methods. There are certain indications that the various forms of tumors are not produced by one organism, or even necessarily by one class of organisms. Thus from one pigmented tumor we have obtained a pure culture of an unknown fungus, which undet certain conditions produces the pigment found in the tumor. We have likewise been able by special methods to stain the elements of the organism in the tumor. The experimental portion of our work we are not yet prepared to report upon.

Every trained laboratory investigator will appreciate the difficulties with which we are confronted in the investigation of a subject whch has so far baffled science, especially as the organisms which we are forced to study, because of their presence in certain tumors, belong to classes with which the pathologist or bacteriologist have as yet had nothing to do, and whose habitat and charac-

teristics are unknown. Only by comparative investigation of all of the species which we are able to obtain, combined with elaborate experimentation, shall we be able to reach definite conclusions regarding the role which these organisms possibly play in the production of malignant neoplasms. Having exhausted conventional methods, we have now entered upon a new field of research, based upon the knowledge which we have been able to acquire of these organisms, and we have already indications which lead us to believe that the difficulties are not insurmountable.

In this work we have endeavored—and have succeeded to a limited extent—to arouse the interest and co-operation of the veterinarians, who come into contact with a large amount of interesting material. To the personal interest of Drs. Wende and Zinc of Buffalo, for instance, we are indebted for some very interesting specimens from animals.

This report is essentially a report of progress, with an earnest request for continuance of the public aid heretofore extended, *without which no such serious investigation can ever be successfully prosecuted.* Within a few weeks we hope to be able to publish in the medical press detailed scientific statements which shall exactly cover some of the work we have already accomplished.

Respectfully submitted to the Legislature of the State of New York by

ROSWELL PARK, *Director*,
M. D. MANN,
CHARLES CARY,
Committee on State Laboratory of the Medical Faculty.

THIRD ANNUAL REPORT

OF THE

NEW YORK STATE

PATHOLOGICAL LABORATORY

OF THE

UNIVERSITY OF BUFFALO.

FOR THE YEAR 1900.

Transmitted to the Legislature April 15, 1901.

ALBANY:
JAMES B. LYON, STATE PRINTER,
1901.

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JAMES B. LYON, STATE PRINTER.
1901.

STATE OF NEW YORK.

No. 63.

IN ASSEMBLY,

APRIL 15, 1901.

THIRD ANNUAL REPORT

OF THE

New York State Pathological Laboratory of the University of Buffalo.

For the Year 1900.

To the Legislature:

The third annual report of the New York State Pathological Laboratory of the University of Buffalo is herewith respectfully transmitted to the Legislature. In brief, it comprises an account of the work done, the expense of conducting the same, certain general references to the mortality rate from cancer, a careful statistical study of the distribution of cancer within the city of Buffalo, made by Dr. Irving P. Lyon, clinical microscopist to the Labora-

tory, and illustrated by a carefully prepared map, which will serve as an example of work which should be undertaken throughout the State, as well as of the kind of study which will give real results in the matter of the topographical distribution of cancer. It includes also two special reports—one from Dr. H. R. Gaylord, actual director of the pathological work; and the other from Dr. G. H. A. Clowes, biological chemist.

Below will be found a tabulated statement, indicating the expense of conducting the Laboratory for the period from February 1, 1900, to February 1, 1901, showing that the total expense for the year has been $14,520.05. The bills and accounts are all on file in the Comptroller's office.

	Equipment.	Stock and material.	Sundry expense.	Salaries.	Total.
1900.					
February	$156 99	$86 14	$108 89	$763 33	$1,115 35
March	34 07	55 72	106 72	713 33	909 84
April	61 22	28 54	63 10	713 33	866 19
May	254 00	80 90	91 25	733 33	1,159 48
June	409 76	221 84	45 00	893 33	1,569 93
July	14 55	9 85	97 50	893 33	1,015 23
August	56 12	20 40	60 00	903 33	1,039 85
September	433 80	59 45	100 00	903 33	1,496 58
October	721 54	61 16	23 82	923 33	1,729 85
November	275 84	104 18	136 29	923 33	1,439 64
December	9 22	51 22	46 44	923 33	1,030 21
1901.					
January	108 40	80 40	35 77	923 33	1,147 90
	$2,535 51	$859 80	$914 78	$10,209 96	$14,520 05

This Laboratory was founded and is conducted for the purpose of studying the disease cancer in all its aspects. The question of the treatment of the disease will come in after something more definite regarding its nature has been established. At present, all our energies are being directed to this particular end. The Laboratory is conducted by a committee of the medical faculty of the University of Buffalo, which has general supervision of its management. Its business accounts and financial statements, as well as its disbursements, all pass through the hands of the chairman of the

committee, with the approval of the Comptroller of the State of New York.

With reference to the frequency of this disease, there is submitted herewith a table made from the monthly reports of the State Board of Health, which shows that the total number of deaths from cancer for the year ending December 1, 1900, was 4,875 an increase of 342 over the deaths during the previous year (1899), whose total was 4,533.

Mortality New York State, year ending Dec. 1, 1900, from—

	Typhoid fever.	Consumption.	Cancer.
1899.			
December	155	1,088	416
1900.			
January	144	1,140	382
February	122	1,131	396
March	120	1,363	443
April	96	1,302	410
May	102	1,285	393
June	65	1,070	397
July	101	1,102	431
August	174	1,047	436
September	245	980	405
October	283	1,078	376
November	233	1,011	390
Totals	1,840	13,597	4,875

Statements made in previous annual reports as to the gradual increase of the mortality rate from cancer, not alone in this State, but in this part of the world, have been on more than one occasion challenged, and efforts have been made to discredit them in various quarters. Nevertheless, the figures themselves, being taken from official sources, must remain and must be believed, as not being open to challenge considering the source from which they were taken. Furthermore, as stated in the last annual report, the general deductions and conclusions arrived at continue to be supported, by evidence from all over the world, that cancer as a disease is on the increase. For instance, in Sweden, the official statistics tabulated by Dr. U. Quensel, of Stockholm, show that the mortality from

carcinoma has risen from 8 to 9.75 per 10,000 inhabitants during the four-year period from 1895 to 1899. He found that twenty years ago the women affected outnumbered the men by 192 to 100, while during this last four-year period the proportion changed to 150 to 100. Twenty years ago, the cancer mortality represented 3.57 per cent. of the total number of deaths. Of late, it represents 6.27. (*Journal American Medical Association*, February 23, 1901, p. 521.)

From England comes still further confirmation of the contention made in previous reports; thus, Thomas Oliver, in *The Lancet* (Nov. 10, 1900, p. 1335), in discussing the question of the heredity of carcinoma, points out that statistics, both in England and in America, show that, while the mortality rate from tuberculosis is decreasing, that from carcinoma is notably on the increase. Thus the mortality records of the Mutual Life Insurance Company of New York, covering the period from 1843 to 1898, and dealing with 46,525 deaths, include 882 due to carcinoma. The age-period in which the largest number of deaths from this cause occurs is from 55 to 60. In 1879 the percentage of deaths from carcinoma between the ages of 50 and 70 was 4.23; in 1889, 6.22; in 1898, 7.59. According to the statistics of the Scottish Widows' Fund, the statistics of the deaths from carcinoma were, from 1815 to 1845, 0.93 per cent. of the whole number; from 1845 to 1852, 0.72; from 1852 to 1859, 2.87; from 1859 to 1867, 3; from 1867 to 1873, 4.56; from 1873 to 1880, 4.34; and from 1880 to 1887, 5.23. Twice as many females as males die from carcinoma, their mean age of death being 62.29 years, as against 60.43 years for males.

From Table 2, it will be seen that the deaths from cancer in this State largely exceed the losses of our troops from all causes during the last war. The question then comes up, if we have in this coun-

try a disease which is so much more fatal than warfare, why not study it as carefully as possible, and from every side; and that, we take it, is the purpose of this Laboratory.

In the way of further illustration of what has been said, take for instance, increase of cancer in Germany as evidenced by the following quotation:

"The steady increase of malignant disease is the dark shadow on recent medical progress. In Germany and England, where the only exact statistics are available, cancer increases *parsi passu* with the decline of consumption. Thus, in the former country, the annual increase of the disease is estimated by Dr. Maeder (Zeitschrift für Hygiene and Infections-Krankheiten, xxiii, p. 235) at 0.17 per 10,000 living. This will, by the end of the century, give a death rate of 22 per 10,000, which is the present consumption mortality of Germany. If by that time the tuberculosis rate is brought down to five, we may congratulate ourselves on having exactly reversed the proportionate destructiveness of the two diseases. There is no reason, however, to suppose any connection between the corresponding rise and fall in the two diseases, for the unfortunate people of Saxony and Baden, though they share in the increase of cancer, have hitherto had no part in the decline of consumption. The fact most clearly brought out by Dr. Maeder's statistics is the influence of locality and of town life. Thus, in Prussia, cancer mortality in towns is more than double that in the country, being 7.9 compared with 3.8 in 1896; and the mortality in the large towns (over 100,000) is relatively greater than in the smaller ones. At the same time, certain towns are specially afflicted, forming, as it were, cancer centres, while others are comparatively exempt. Thus, there are relatively more than twice as many deaths from cancer in Stralsund and Schleswig as in Treves and Coblentz."

(N. Y. Medical Record, March 16, 1901, p. 437.)

Again, in the Philadelphia *Medical Journal*, March 16, 1901, p. 498, is the following on the treatment of cancer:

"Professor L. Lewshin remarks that during the last 33 years of his surgical practice, no material improvement has taken place in the treatment of cancer. The percentage of complete recoveries following surgical intervention, as attested by European surgeons, is still very small, even in operable carcinomas. On the other hand, the statistics of Massey, Heyman, Czerny, and others, establish beyond doubt the alarming fact that cancer, especially of the digestive organs, is on a progressive increase. In Moscow there occurred in 1880, 411 deaths from cancer; while in 1896 the number of deaths from this disease reached 892, almost doubled. It is to be regretted that the author does not state the extent of the increase in population during the same period; but it may be assumed that he has taken this into account in making his deductions. To the hundreds who die, there are thousands who drag out a miserable existence, a burden to themselves and their families and a ready prey to the quack. These unfortunate sufferers should be taken care of. Moreover, the rapid increase of an incurable and fatal malady renders of paramount importance the study of the disease in all its phases. Both the humanitarian and scientific purposes could only be accomplished by the establishment of proper sanitaries. Such an one is being established in Moscow through the efforts of Professor Lewshin, who has already received private contributions to the amount of 300,000 roubles (about $150,000). The city council of Moscow pledged itself to pay for the maintenance of 50 patients for 10 years, while the medical faculty of the Moscow University has taken the sanitarium under its protection as an addition to the university clinics."

When this Laboratory was founded, the medical department of the University of Buffalo gave it every possible accommodation which its own restricted space would afford. The needs of the work have, in a short time, entirely outgrown the space at command, and the faculty felt it extremely necessary to secure other and larger quarters if this beneficent State work were to be carried on under their

auspices. It will be an evidence of the fact that, in the city where it is located, the character of this work has so strongly appealed to our citizens, that a most generous response has been made to efforts to secure a separate building for this sole purpose. It was felt that the faculty could, with the greatest propriety, ask the citizens of Buffalo to erect a building adequate for the purpose, on the expectation, and with the hope, that the State of New York would continue to appropriate the necessary funds for its maintenance and the conduct of the work. Generous friends of the University have contributed the funds for this purpose, and a building is now in course of erection with every prospect that it will be completed by midsummer. It will be known as the Gratwick Research Laboratory, in honor of the principal contributor to the fund. It is situated on High street, directly opposite the General Hospital, in which numerous cancer cases are always to be met. It has been found that the relations between the laboratory work and the clinical study of these cases cannot be too close, and the effort was deliberately made to put the building in the closest proximity with the hospital where so many of these cases abound, for reasons which are set forth in Dr. Clowes' report, submitted herewith, which will demonstrate the advantage to be gained by this proximity. Sketches of the ground plan and elevation of the Laboratory are presented herewith, through the courtesy of the architect, Mr. George Cary, of Buffalo. They will show a building in which ample accommodation has been made for the pathological, the bacteriological and the chemical study of this disease, as well as for the clinical and experimental work connected with it. The University has felt that it could in no wise better justify its own earnestness and interest in the continuance of this work than by the erection and completion of this building.

The past year has been characterized by steady plodding work along the lines which seem to be absolutely necessary if real progress were to be made. The question of cancer has always been the pathological mystery of ages, and is the most important one now before the medical world. It is with the keenest satisfaction that we now place before the Legislature the preliminary report of Dr. Gaylord, in which he voices the statement that not only may cancer now be regarded as positively a parasitic disease, but that the actual cause of the disease has been recognized in this Laboratory. This statement is in the light of a discovery so recently made that this report has been delayed in waiting for sufficient information upon which to base its nature. Experts all over the world have united in the belief that this question when solved would be reached by research such as has always been within the scope of, and comprehended by the work of this Laboratory. This work has attracted attention from the leading scientists of the world. Its management has been offered a position upon the committee appointed by the German physicians for the investigation of this disease in Germany. It has led also to remarkable development of technique, which has come about in obedience to the necessities of the work, some of which is beautifully illustrated in photographs and color work of Dr. Gaylord, which are also transmitted herewith. Hitherto it has not been possible to convey to others such exact and favorable reproduction of work done as is furnished by these illustrations. They are here introduced as specimens of work actually accomplished.

The committee charged with the conduct of this work desire to express their appreciation, not only of the assistance offered by the State and the readiness with which their efforts have been seconded by State officials, but also their appreciation of the faithful and ear-

nest work of the gentlemen now composing the staff of the Laboratory, which staff is made up as follows:

Dr. H. R. Gaylord, in charge of the work, Pathologist;

Dr. G. H. A. Clowes, Biological Chemist;

Dr. Irving P. Lyon, Clinical Microscopist;

Dr. H. G. Matzinger, Bacteriologist,

with a sufficient corps of assistants to enable this work to be more rapidly conducted so soon as the new laboratory building is completed.

In view of the discoveries recently made, and of the almost bewilderingly large field for research which is thus newly opened up, we feel that our duty to the work impels us to ask a little more from the State than it has yet done for us. By reference to Table 1, it will be seen that the appropriation made last year was just about adequate for the purpose for which it was intended. With less, the work would have been seriously crippled. Now, in view of the fresh possibilities of research and discovery, the committee would like to employ more skilled assistants with better library facilities than are at present enjoyed. If the amount of last year's appropriation might be increased by $5,000 or $10,000, we sincerely feel that it would be money well invested, and would yield a brilliant return. We, therefore, respectfully ask that the appropriation for conducting the institution for the ensuing year be made at least $20,000.

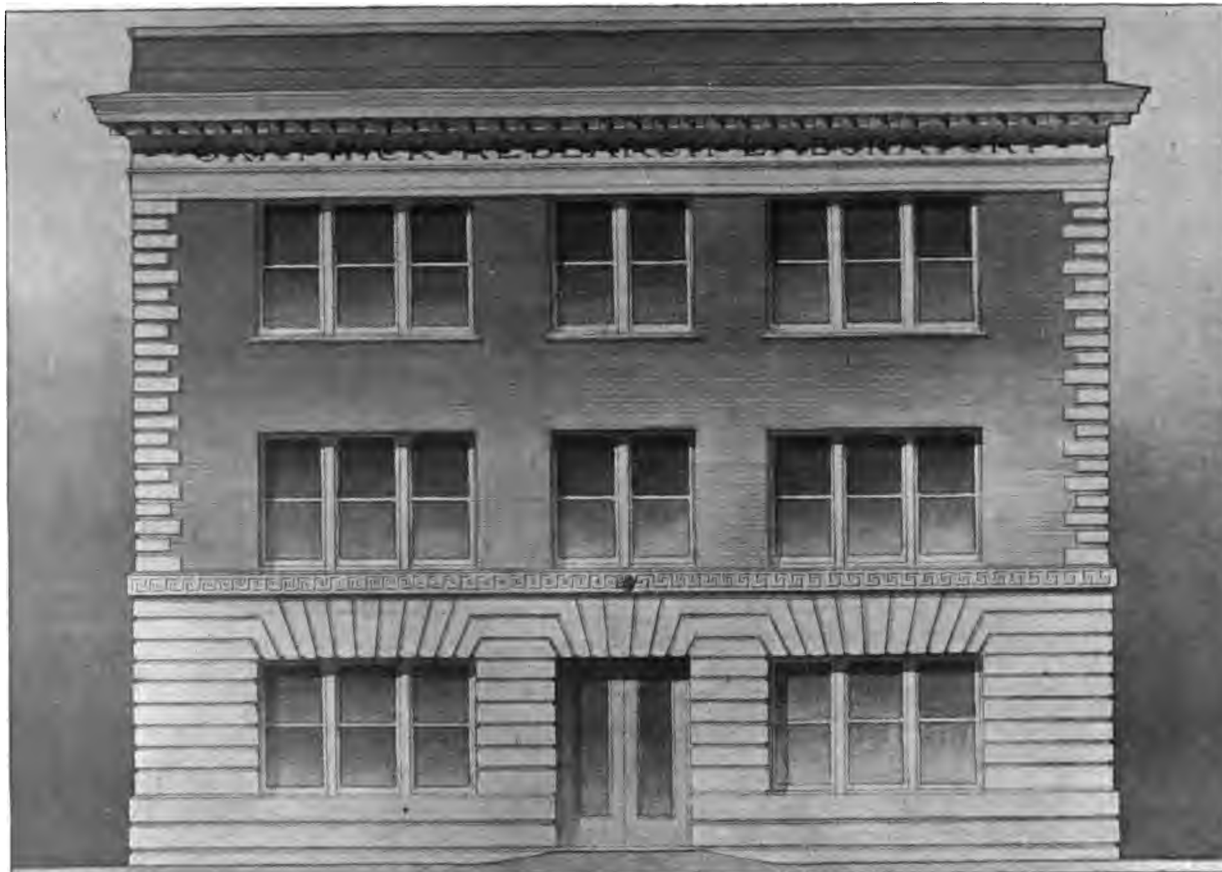
Very respectfully,

ROSWELL PARK,

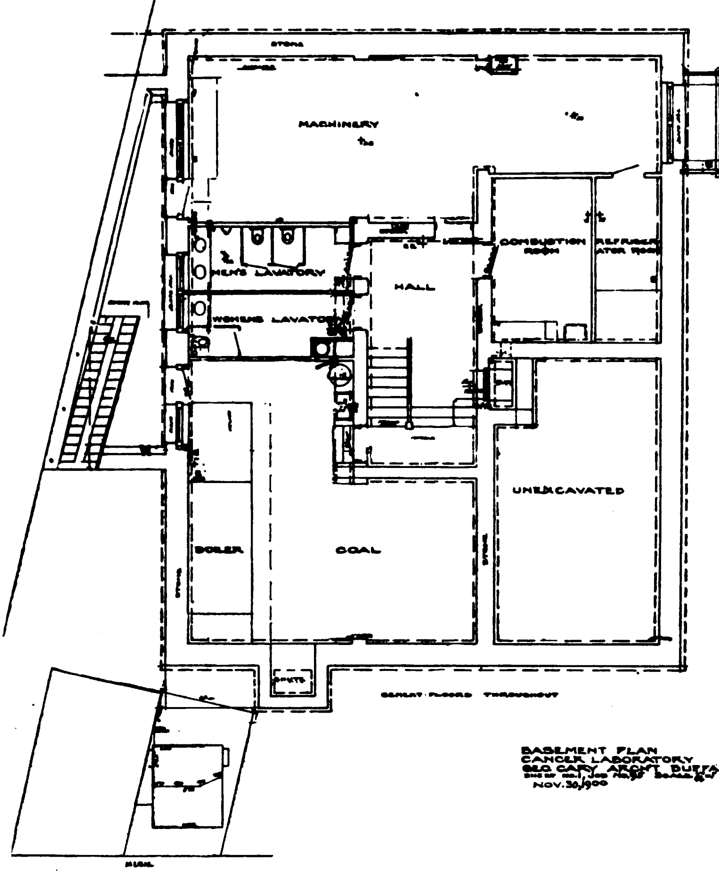
MATTHEW D. MANN,

CHARLES CARY,

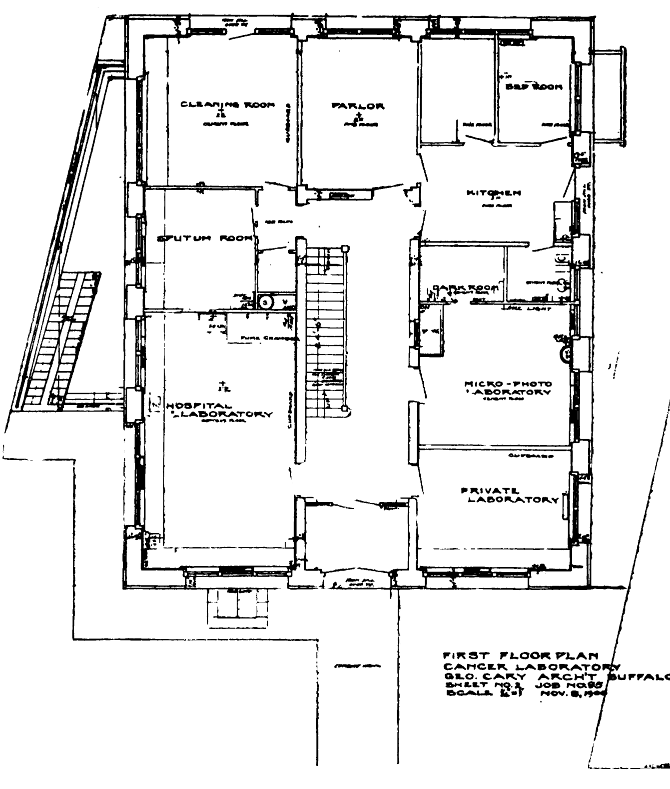
Faculty Committee.



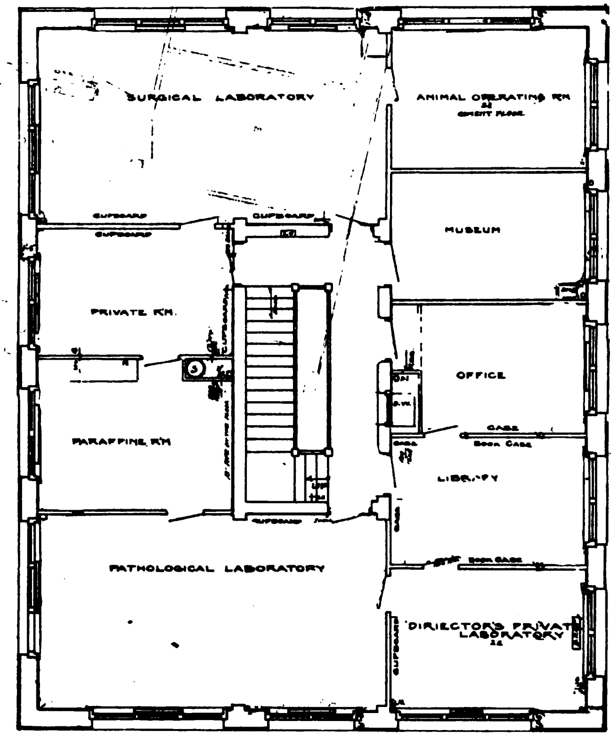
FRONT ELEVATION.



BASEMENT PLAN
CANCER LABORATORY
GEO CARY ARCH'T BUFFALO
NOV. 30, 1900



FIRST FLOOR PLAN
CANCER LABORATORY
GEO. CARY ARCH'T BUFFALO
SHEET NO. 2 JOB NO. 95
SCALE ¼"=1' NOV. 8, 1900



SECOND FLOOR PLAN
CANCER LABORATORY
GEO. CARY ARCH'T BUFFALO
SHEET NO. 3 JOB NO. 95
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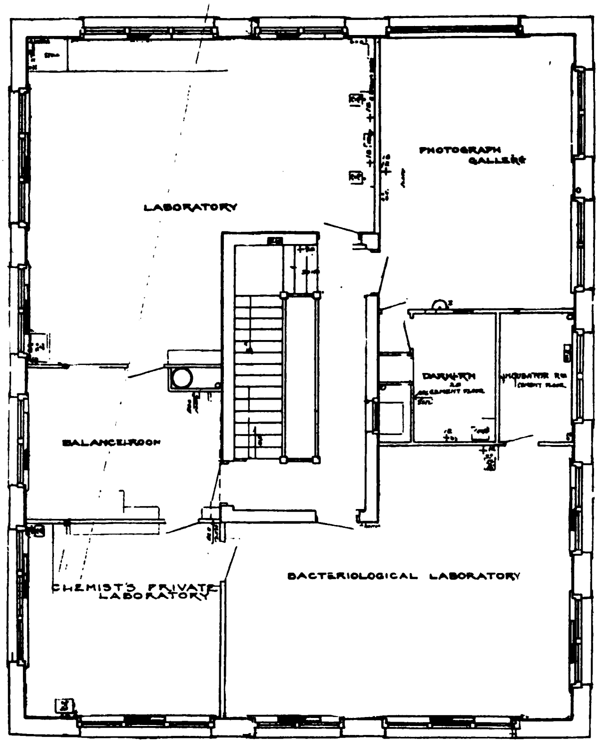
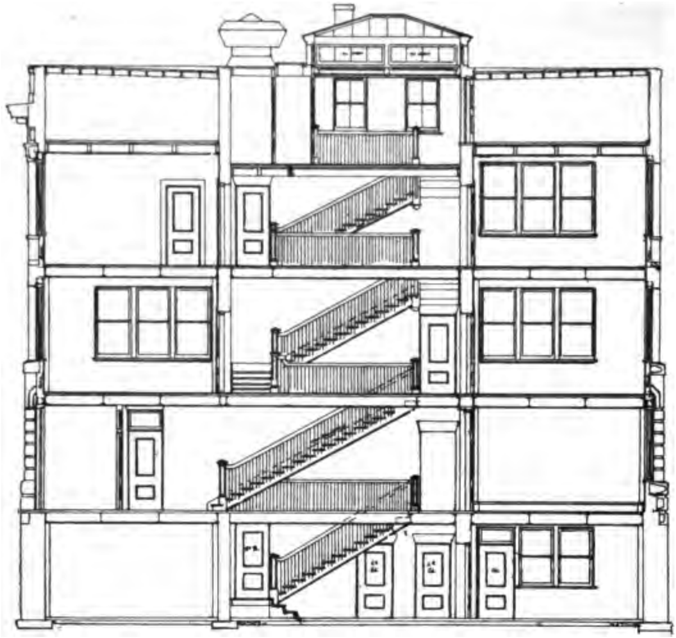
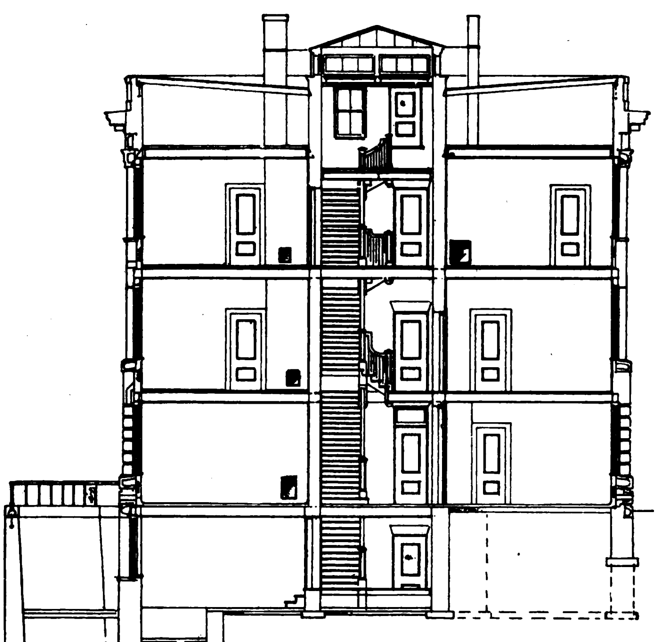


THIRD FLOOR PLAN
CANCER LABORATORY
GEO. CARY ARCH'T BUFFALO
SHEET NO. 4 JOB NO. 95
SCALE ¼"=1' NOV. 6, 1900



LONGITUDINAL SECTION
CANCER LABORATORY
GEO. CARY ARCH'T BUFFALO
SHEET NO. 8, JOB NO. 95
SCALE 1/8"=1' NOV. 8, 1900



CROSS SECTION
CANCER LABORATORY
GEO. CARY ARCH'T BUFFALO
SHEET NO. 7. JOB NO. 95
SCALE 1/8"=1' NOV. 7, 1900

ON THE PRESENCE OF A CHARACTERISTIC ORGANISM IN CANCER—PRESUMABLY A PROTOZOON.

A Preliminary Report Based Upon Three Years' Work in the New York State Pathological Laboratory.

By Harvey R. Gaylord, M. D.

In January, 1899, at a meeting of the Medical Society of the State of New York, in Albany, the writer made a statement regarding certain observations made by himself in the State Pathological Laboratory. As these remarks appear in the transactions of this Society, they are essentially as follows:

" Others have found organisms in cancer and have explained them as protozoa. Sanfelice and all observers of alleged parasites in cancer have noted the great variability of these forms in the tissue. As a result of our preliminary work, we think we have discovered the reason for this. We owe to Busse the knowledge of the fact that all staining methods are unreliable for such research. We therefore worked with the fresh methods, altough we found at first that it was very confusing. We have discovered in all the cases of cancer so far examined that by fresh methods the organisms can always be found. These bodies resemble fat in the fresh state. It was only when we applied the ether test and the osmic-acid that we discovered that they were not particles of fat. We next discovered that we could crack

their edges with the coverglass. There was no reason, even then, to believe that these might not be unusual forms of fat. We next injected them into the abdominal cavities of animals. Most of the animals developed peritonitis, and large quantities of these bodies could be obtained from the peritoneal fluid. In the last few days we have observed the round form developed under the coverglass. They can be found in every cancer if properly sought for, and can be injected into animals and be recovered. They also changed their form.

" We would not have made these statements were it not for a remarkable experiment at the beginning of this work. Dr. Park had a case of abdominal carcinosis. An exploratory incision was made, and a quantity of serum from the abdominal cavity was given to me for investigation. It was in this fluid that we first found these bodies, and observed that they did not increase. After the fluid had been kept in the thermostat for three weeks we could still find the same bodies. They were then injected into the jugular vein of a guinea-pig, and three weeks and a half afterward, on killing the animal, we found a primary adeno-carcinoma of the lung. This experience, we may say, is unique. The fluid had been carefully sedimented, and the fluid for inoculation taken from the top, so that it was not at all probable that cancer cells were actually introduced into the animal. In the case from which the fluid was taken, the growth was a colloid carcinoma, but this was not the form of cancer which developed in the inoculated animal. It is also to be noted that carcinoma in the guinea-pig is extremely rare."

Since the period of this statement, our attention has been principally turned to an investigation into the nature of these parasites, in attempts to demonstrate them in the tissue, and in attempts to cultivate them. The following is a detailed report of the experiment:

Case 1. S. N., male, aged 51, a patient of Dr. Park. He was seen at his home, and presented physical signs of a large intraperitoneal tumor. The patient was removed to the Buffalo General Hospital, where an exploratory operation was performed by Dr. Park, August 12, 1898. Preparations had been previously made to collect aseptic fluid in sterile tubes and flasks, Dr. Park opened the distended abdomen with the usual aseptic precautions, and a sterile tube was inserted in the opening and about half a liter of the fluid was permitted to flow into a flask. Then three test tubes in succession were held beneath the running tube, and the remainder of the fluid was drawn off in separate flasks. The fluid which was removed from the peritoneal cavity was slightly blood-stained, but did not coagulate. The three tubes, labeled *a*, *b* and *c*, were immediately placed in the writer's inside vest pocket and were carried warm to the Laboratory, where they were placed in the thermostat. The flasks were not treated in this manner, but were allowed to fall to the room temperature and were not incubated. Inoculations upon bouillon, sugar water and acid sugar water, as well as agar and blood serum were at once made from all three tubes. A careful microscopic examination was likewise made of the peritoneal fluid, which was found to contain a few blood corpuscles and some pale spherical bodies, in size varying from two to ten micromillimeters. They were homogeneous, of pale, yellowish green color, and at first were mistaken for fat droplets, although on closer examination their refractive index was seen to be too low. They were likewise resistant to ether, even when the fluid or tissues containing them were first treated with potassium hydrate, then centrifuged, washed in water, treated with 60, 80, 95 per cent. and absolute alcohol, washed in absolute alcohol and ether, equal parts, and then placed in an ether

extractor for four days. When treated with osmic acid, they failed to give the black reaction which characterizes fat. Attempts to stain them were partly successful, and it was found with coverslips fixed by heat, that, although the bodies were greatly deformed by the process, a certain number of them could be stained with carbol-thionin or the usual aniline dyes. Some of these bodies, though not very numerous, contained granular material which showed marked Brownonian movement. The tubes were examined from day to day, and we were able to demonstrate that these spherical bodies gradually increased in size, became more indefinite and gradually lost their yellowish green color. As they increased in size, they apparently became more fluid and commonly sent out pseudopods and long projections. Fine colorless granules appeared in the protoplasm, and in some a delicate nucleus could be made out. Ultimately the larger forms of the organisms became transformed into what appeared to be large sacs containing highly refractive granules and small spherical bodies, not unlike the free spherical bodies above described. The membrane of the sac was demonstrable as a pale colorless structure. The diameter of these sacs was on the average about 20-25 micromillimeters, or the size of a good-sized epithelial cell.

August 19th, 3 ccs. of tube *a* were injected into the peritoneal cavity of a female dog. August 20th a fine surface growth was noted in tubes *a* and *b*, of a small organism about the size of a coccus, which presented a peculiar bud-like growth, and which resisted all attempts at cultivation. On August 25th 3 ccs. of fluid from tube *c* was injected into the jugular vein of a full-grown guinea-pig (Pig 1). August 26th 4 ccs. of the same tube was injected into the peritoneal cavity of a second guinea-pig (Pig 2).

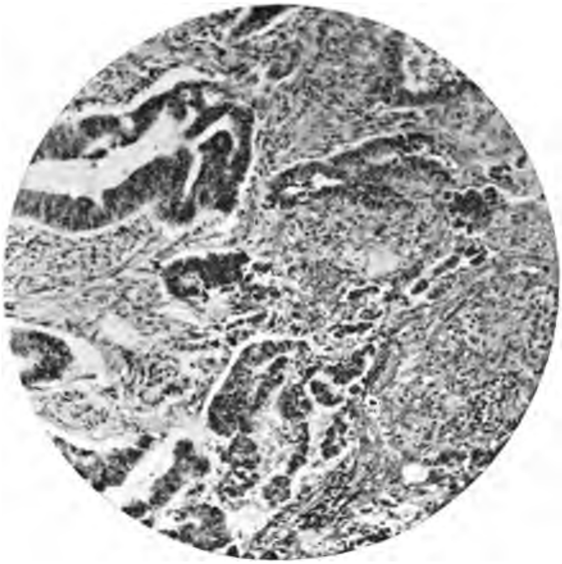
On August 29th, the patient, who, since the operation, had not been doing well, died. Unfortunately the autopsy was begun by the attending physician, who opened the abdominal cavity and had already contaminated its contents before the peritoneal fluid was collected. The following is extracted from the autopsy notes:

"Autopsy, four hours after death. Body of a well formed, middle-sized man. Muscular structure well developed, skin pale, fat scanty. Peritoneal cavity contains a large amount of sero-sanguineous fluid. The peritoneum is greatly thickened, contains a large number of translucent vesicles, which are likewise scattered over the entire peritoneal surface, including that of the liver and the under surface of the diaphragm. The pelvic cavity is entirely filled with these gelatinous masses. On removing the enlarged omentum, it is found to measure 95 cm. in the long axis. Its greatest thickness is 12 cm. After removing the omental tumor, the intestines are apparently free, except a large encapsulated mass of gelatinous material near the ileocaecal junction, apparently involving the lumen of the intestine. Intestines are removed without difficulty, when the tumor in the neighborhood of the caecum is found to be firmly attached to the peritoneal wall, is apparently of a cystic nature, and contains a mass of gelatinous material. On opening the intestine no connection between the lumen of the caecum and the tumor mass can be detected. The tumor mass, however, involves the appendix, which is obliterated. The spleen is dark red in color and weighs 4 ounces. The right kidney is embedded in a mass of gelatinous material. The capsule of the kidney strips easily, the diameter of the cortex is 5 mm., of grayish rose color. The papillae are anaemic. Kidney pelvis unchanged, Left kidney same as right. The gelatinous material in the pelvis fills in the space between the rectum and bladder. The entire under surface of the diaphragm

is thickly infiltrated with gelatinous vesicles. The liver is adherent to the diaphragm, and the suspensory and round ligaments are thickly infiltrated with gelatinous material. The gall bladder is distended; the gall duct, patulous. On section, the liver presents a typical nutmeg appearance, and the substance of the organ is apparently not at any point invaded by the gelatinous material. On opening the thoracic cavity, the lungs extend well forward, pericardial sac contains a small amount of clear, straw-colored fluid. On opening the pericardium, the heart is somewhat small, the heart muscle of a pale brownish color. In the right ventricle is a large rose-colored clot, which extends into the pulmonary artery. The lungs contain a normal amount of air, show grayish and red mottling, but no evidence of metastases. Projecting into the left pulmonary artery is a large thrombus, adherent at various points and extending into the branches of the pulmonary artery. The bronchi contain frothy exudate. The right lung presents the same characteristics as the left, and the right pulmonary artery likewise contains a thrombus. The transverse and descending aorta shows a moderate amount of sclerotic change. The bladder and genitourinary tract are free from abnormalities. The omentum and the cystic mass attached to the caecum were removed and preserved for further examination."

Anatomical diagnosis.—Colloid carcinoma of the peritoneum; thromboses of the pulmonary arteries; atheroma of the aorta; brown atrophy of the heart muscle.

The microscopical examination of the fresh material from the vesicles of the tumor showed it to consist of a finely granular or homogeneous material containing a considerable number of degenerated epithelial cells and the small spherical bodies noted in the peritoneal fluid. Examination of the peritoneal fluid from the



1.
Adenocarcinoma. Case I. (M. P.) (H. E.)

2.
Colloid mass from under surface of liver. Case I. (M. P.) (Methylene blue.)

cadaver showed that it likewise contained large numbers of the various forms of the organism. Portions removed from different parts of the tumor were hardened in various hardening reagents. The examination of the hardened and stained sections showed the tumor to be an adeno-carcinoma of the omentum, which had undergone advanced colloid degeneration. The gelatinous vesicles showed the typical appearance and characteristics of colloid carcinoma. They penetrated between the muscle fibres of the diaphragm into the layers of the capsule of the liver and involved the entire thickness of the omentum. The muscle fibres or connective tissue structures were forced apart by the gelatinous material.

In the neighborhood of the caecum, the colloid degeneration of the intestine was not so marked as in the other portions. Here the epithelial structures could be seen invading the abdominal wall and the mass of adherent structures which surround the growth. The description of a section from the growth in the neighborhood of the caecum and one from the colloid portions of the tumor will include the principal characteristic features.

(Slide 2.) A section taken from the region of the primary tumor, hardened in alcohol, stained with Delafield's haematoxylin, includes a portion of the sub-peritoneal fat and the wall of the tumor. The connective tissue stroma of the section is thickly infiltrated with round cells. In the deeper portions of the section are a number of muscle fibres, likewise infiltrated with round cells. Extending through the entire thickness of the section are large, epithelial, glandular structures and nests of isolated cylindrical epithelium. (See Plate I, Fig. 1.) Near the surface of the tumor these glands are broken up, and the epithelium is scattered through the stroma without definite arrangement. The cylindrical form of the epithelium is likewise changed, and here and there concentric structures closely

resembling epithelial pearls may be noted. In the large glandular structures the epithelium is commonly several layers deep. The nuclei are large, deeply stained, of irregular form and irregularly placed. The protoplasm of the cells stains deeply. Karyokinetic figures are uncommon. When examined under high power, a number of the cells are found to contain typical Plimmer inclusions and the various forms beginning with small spherical bodies known as Russell fuchsin bodies, and certain deeply stained bodies within the nuclei and protoplasm of the cells, which we now recognize as the younger forms of the parasite. A portion of the tumor covering the under surface of the diaphragm, the surface of the liver and the peritoneal surface, which shows the typical vesicle formation characterizing this growth, reveals, on microscopical examination, the typical appearances and structure of an adeno-carcinoma in an advanced stage of mucoid degeneration. The description of a single slide will suffice.

Slide 10, from material hardened in Fleming's mixture, embedded in paraffine and stained with iron haematoxylin Bordeaux red, through a mass of gelatinous material from the under surface of the diaphragm. Tumor is divided into large vesicular structures, which, under the microscope, are divided up into smaller vesicles. These are filled with coagulated material, in which are embedded a number of epithelial cells in various stages of mucoid degeneration. The nuclei of these cells are somewhat smaller than those seen in Slide 1. In some of the vesicles the cells are of a typical cylindrical type, arranged in rows in the usual manner found in adeno-carcinoma. Nearly every cell contains a large vesicle apparently filled with mucoid material. In some of the vesicles the cells are scarcely discernible, only occasional chromatin granules and indefinite masses of protoplasm marking the site where the cells once existed. The

stroma is thin, contains but few nuclei and occasionally, at the intersections, a few fat cells and a well-defined round-celled infiltration. The nucleus of nearly every cell contains a deeply stained body (nuclear infection). The occasional vacuoles filled with mucoid material present an entirely different appearance from possible Plimmer inclusions.

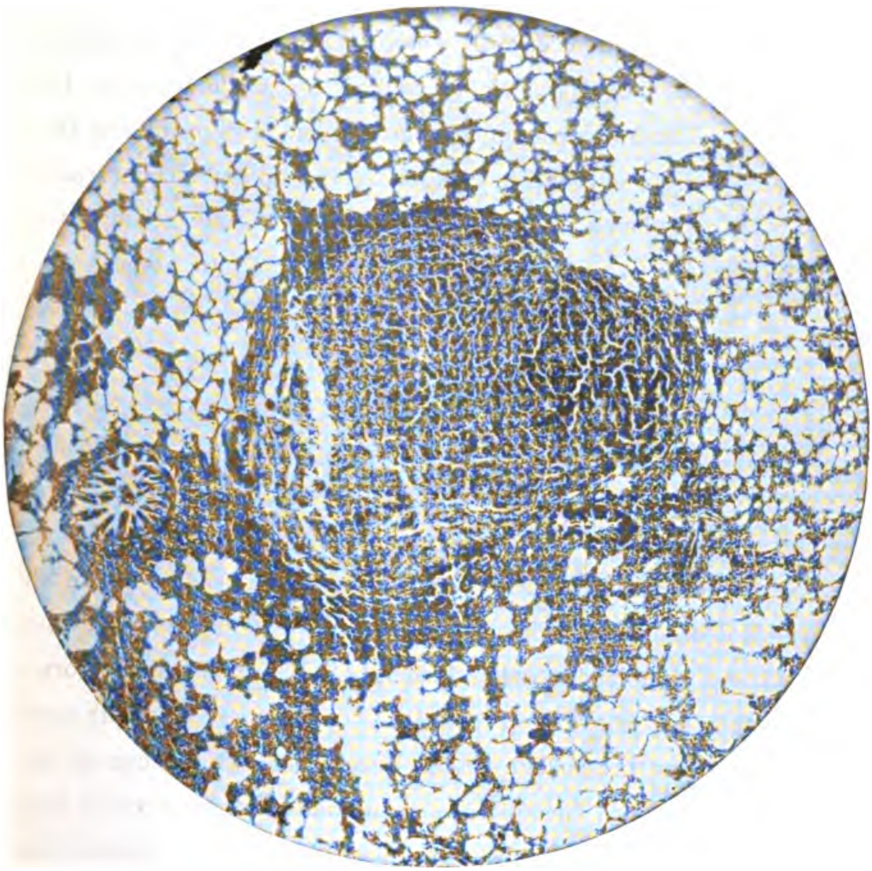
Slide 12, taken from a mucoid portion of the tumor, near the site of the original tumor. Material hardened in sublimate, stained with methylene blue. The tumor is made up of large and smaller vesicles filled with mucoid material. Within the vesicles may be seen the remnants of adenomatous structures, the epithelium of which shows marked mucoid degeneration. Under high power the cells of this portion of the tumor are found to closely resemble the adenomatus structures seen in Slide 2.

Slide 13. Section of a large mucoid mass removed from the under surface of the liver, stained with methylene blue. The vesicles of this section contain deeply stained masses of mucoid material. These are sharply delimited against the underlying structures. Embedded in the material are the fragments of degenerated epithelium. No well-preserved epithelial elements are present. (See Plate I, Fig. 2.)

Cultures made from different portions of the tumor were all bacteriologically negative. The usual forms of bacteriological culture media were employed. These were placed under aerobic and anaerobic conditions.

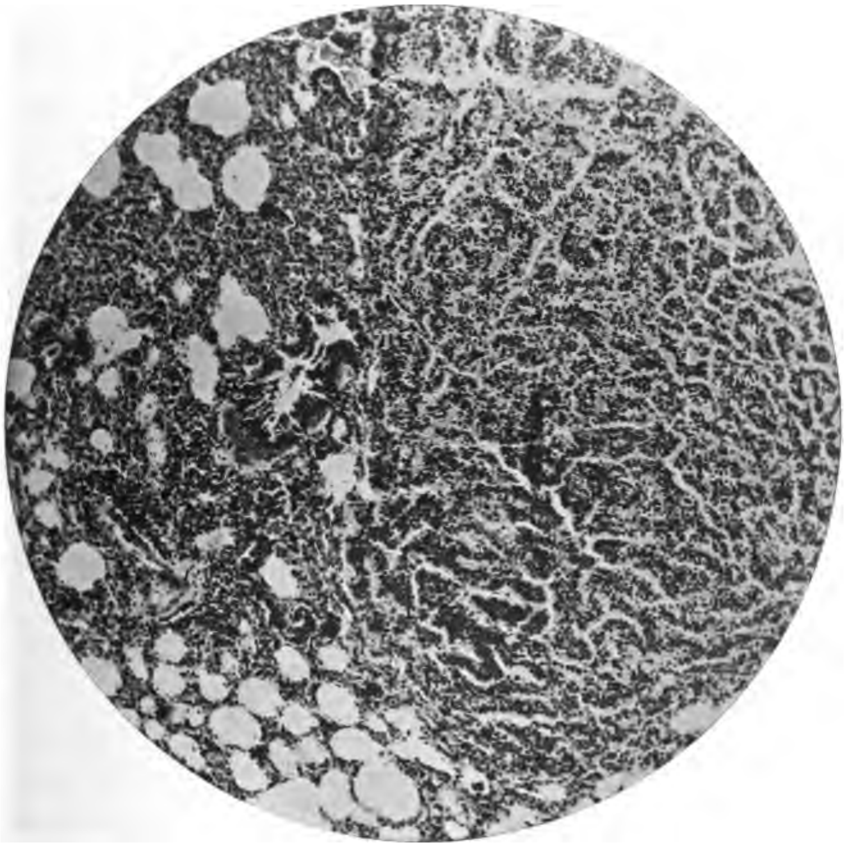
On the 6th of September the following note appears in the Laboratory Journal: "Guinea pig No. 1 shows distinct evidence of listlessness and does not appear well. The animal sits in the corner of its cage and does not move about." On Wednesday, October 14th, both Pigs 1 and 2 were killed. The following notes taken from the autopsy of Pig 1 will be of interest:

"Inspection of the site where the injection of the serum was made in the right jugular shows that the superficial wound has healed, and at the point of ligation the jugular vein is transformed into a fibrous cord. On opening the thoracic cavity nothing of interest is to be noted until the lungs are reached. These are found to contain a normal amount of air. The pleura appears slightly injected. On opening the pleural cavity cultures are made from the lung surface. The lungs contain a large amount of pigment and show areas of venous engorgement with occasional minute haemorrhages beneath the pleura. After removing the lungs and incising them, both are found to contain a large number of minute nodules varying from the size of a pinhead to one larger than the rest, about the size of a grain of rice. These nodules are white, of greater consistence than the lung tissue, and somewhat elevated above the cut surface. Careful examination shows them to be located near or surrounding the small bronchi. The small areas of haemorrhage noted on opening the thoracic cavity are found to be confined to the region immediately beneath the pleura. On examining the abdominal organs the stomach is found to be empty, the intestines collapsed, the bladder widely distended with urine, and the cortex of each kidney is of a deep red color. The capsules strip with some difficulty, and the stellate vessels directly beneath the capsule are slightly injected. The spleen is somewhat enlarged, shows a mottled, bright red and reddish-brown appearance. On incision, the follicles are unusually large and stand out plainly against a background of deep red and reddish-brown pulp. Fresh microscopical examination of the heart's blood shows it to contain, besides the normal constituents of the blood, a large number of small, spherical, highly refractive bodies closely resembling fat, which, in size and appearance are identical with those found



Section of Lung, Pig I, including the largest nodule. Primary Adenocarcinoma following injection of protozoa in peritoneal fluid of Case I. (Low Power.) (Hæmatoxylin Eosin.)

PLATE III.



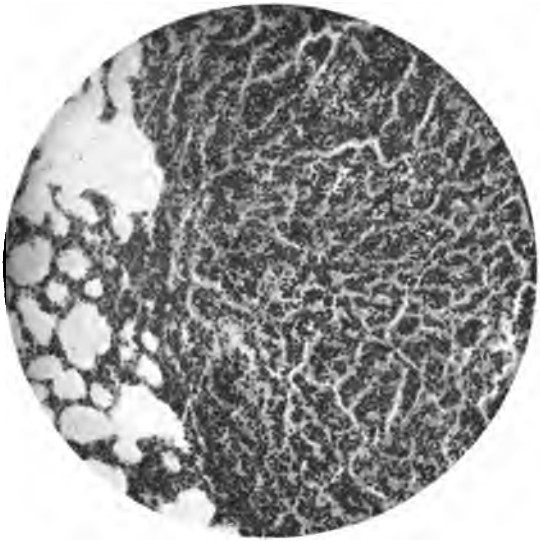
Margin of nodule (Plate II) showing origin of tumor from epithelium of bronchus. (Middle Power.)

in the original fluid with which the animal was injected. Aside from the minute white nodules in the lung, the pigmentation and enlargement of the follicles of the spleen and lymph nodes, and the injection of the kidneys, the remaining organs of the animal show no abnormalities. The lungs were hardened in formaline."

A large number of sections were cut, some of which include the largest nodule above mentioned. On examination with low power, of a section stained with Delafield's haematoxylin, the nodule is readily found by the deep staining of the structures which compose it. On closer scrutiny, even with low power (see Plate II), the structure presents the appearance of a rapidly growing nodule possessing a definite structure. The lung trabeculae in the immediate neighborhood, especially in the portion adjacent to a bronchus show marked interstitial thickening. In the immediate neighborhood is a section of a middle-sized pulmonary vessel and a good-sized bronchus. The remains of a collapsed bronchial artery are seen just at the periphery of the growth. The alveoli of the lung show marked concentric flattening about the periphery of the nodule. A few yellowish-brown spots indicate the presence of pigment within the growth. Under high power the structure of the nodule becomes distinctly apparent. (Plate III.) It is made up of epithelial cells arranged in a characteristic manner upon a delicate connective tissue stroma. This forms the axes of longer and shorter papillary projections, which are closely packed together. Upon these are arranged single and double rows of cylindrical epithelium. At the periphery of the growth, the alveoli of the lung are concentrically flattened, and the structure of the adenoma merges gradually into the structure of the lung trabeculae. In one or two points the adenoma is spreading into the surrounding tissues, and in these localities the trabeculae of the lung show a marked thickening and a distinct round-celled infiltration.

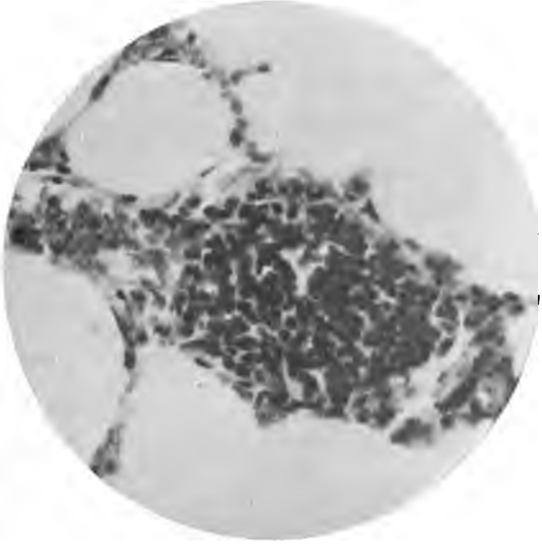
Under still higher power, the nature of the epithelial cells may be more distinctly observed. They are fairly uniform in size, the cell protoplasm is abundant and palely stained. The nuclei are oval, are placed near the base of the cells and stain deeply. The cells are cylindrical in form, but at the periphery, where the compression is great, they show evidence of considerable distortion. Included within the tumor are a number of cells containing coal pigment, and in the stroma are a few capillaries containing blood cells. In the neighborhood of these capillaries are occasional connective tissue cells loaded with haematogenous pigment.

The bronchial vessel lying directly at the margin of the growth is collapsed; the intima shows proliferative changes; the media is somewhat thickened. The adjacent pulmonary vessel is surrounded by a thick layer of cells, which apparently spring from the adventitia of the vessel. These are the typical round-celled variety, and in certain portions are accumulated in groups, forming well-defined nodules. Careful scrutiny of the surrounding pulmonary tissue, especially that portion in which there is great thickening of the trabeculae, shows this change to be due to a proliferation of the connective tissue stroma of the lung. A large number of cells closely resembling the *epithelial cells of the lung are mixed with these.* A certain number of the last mentioned elements contain deposits of coal dust. An examination of the other pulmonary vessels of the lung reveals the same proliferation of the adventitia, and many of the smaller vessels are surrounded by nodes or rings of closely packed round cells (Plate IV, Fig. 2). In various other portions of the lung are areas in which the trabeculae are thickened or the alveoli completely obliterated. Within these areas will be found nests of epithelium, and in the larger, well defined adenomatous structures identical in appearance with that of the largest nodule. (Plate IV, Fig. 1.)



1.

Margin of smaller nodule, Pig I. (M. P.) (H. E.)

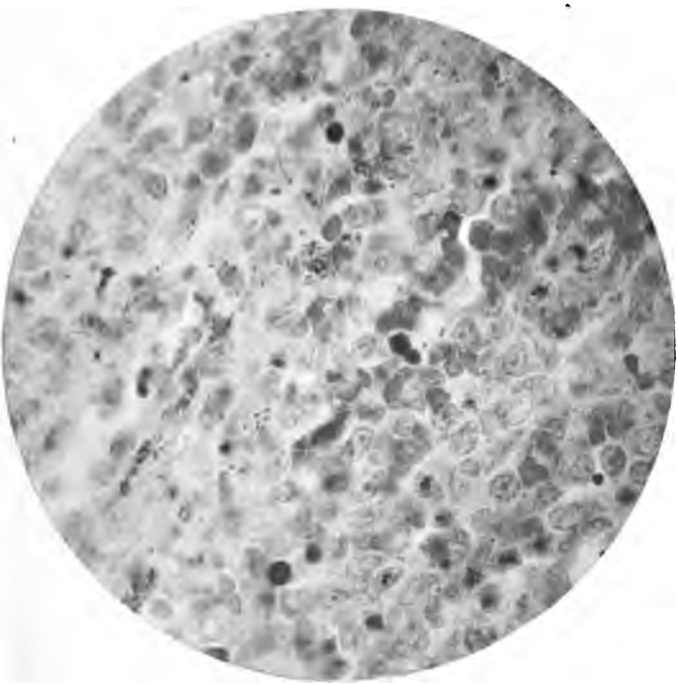


2.

Typical focus of round cells in perivascular lymph space of small vessel. Lung Pig I. (H. P.) (H. E.)

1.

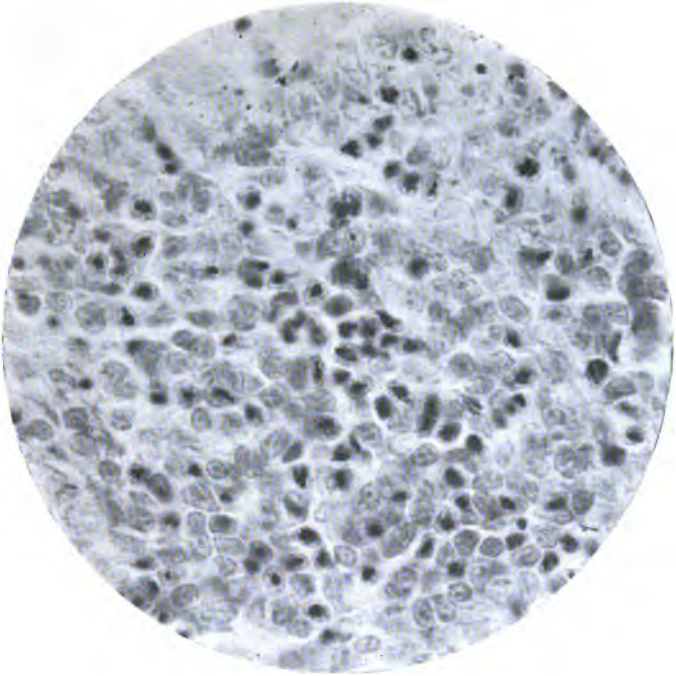
Section of spleen, Pig I, showing enlarged follicles and hæmatogenous pigment deposited in pulp. (L. P.) (H. E.)



2.

Periphery of follicle of spleen, Pig I, free Russell's bodies (young protozoa) between the cells. (H. P.) (Plimmer's method.)

PLATE VI.



1.

2.

3

4.

Since the acquisition of Plimmer's method, we have restained sections of this case, and find that every epithelial cell in the nodule contains a deeply stained nuclear body, which we now recognize as young parasites. The lung trabeculae are infiltrated with large numbers of young organisms, which can only be recognized from round cells by their form and homogeneous nature. They are either round or oval, or appear to have been hardened in the act of projecting pseudopodia. In some cases they are closely packed together, and a considerable number are found in the blood vessels. By carefully investigating the different parts of the lung, it will be found that the epithelial infection, although present wherever nests of epithelium are formed, is not uniform, and that certain bronchi and areas of the lung have escaped. By such a comparison, we may rule out the possibility of these bodies being due to a peculiarity of the staining method, and a careful comparison of a large number of sections shows that the presence of these bodies in certain localities, especially in the carcinomatous nodule holds for all the sections made, although the staining method may have been slightly modified. Directly beneath the pleural surface are areas in which the alveoli are filled with blood and the capillaries are markedly engorged. These areas correspond to the small haemorrhages observed macroscopically.

Examination of sections of the spleen shows it to contain a large amount of brown pigment deposited in the pulp. Evidence of wide-spread haemorrhage is also found, and the follicles are markedly enlarged. (Plate V, Fig. 1.) In sections stained with Plimmer's method, the nuclei of a large number of the cells of the follicles contain deeply stained central bodies, in some cases spherical, in other cases of irregular shape. These we believe are young parasites. (Plate VI, Fig. 2.)

We are led to this interpretation of the bodies within the nuclei in the cells of the follicles for the reason that they were present in the fresh state, where they so closely resembled the extra-cellular forms that we are inclined to place this interpretation upon them, although it must be frankly admited that in such a case it is impossible to absolutely prove the point. Their presence in the fresh state definitely removes the possibility of their being an artifact due to the staining method. If there were not well-known precedents for accepting the idea of a nuclear infection, i. e., the organism caryophagus, etc., we should naturally avoid an expression of opinion. Similar bodies are also found within the nuclei of the epithelial cells of the cornea after inoculation with the vaccine organism. (See Plate XIII, Fig. 2.) See also Gorini, Centralblatt für Bacteriologie, part 1, Vol. XXIX, No. 14.

The pigment in the pulp takes the form of triangular and irregularly shaped plates, and is very abundant. The pulp contains a large number of lymphocytes and red-blood corpuscles. Scattered between the cells in the pulp are a large number of extracellular parasitic bodies, which conform in size to the pale forms which in the fresh state are capable of sending out pseudopodia. (Plate V, Fig. 2.) (Plimmer's stain.)

Summary of Case 1.—The facts in this case may be summarized as follows:

The primary growth was adenoma-carcinoma, probably having its origin in the appendix. This had spread, involving the greater portion of the peritoneal surface, with infiltration of the omentum and mesentery. The greater portion of the tumor had undergone mucoid degeneration, and the peritoneal cavity was filled with clear, straw-colored fluid. The patient was opened aseptically. A tube full of this fluid, which was removed through a sterile tube, and

which remained bacteriologically sterile after an incubation period of thirteen days, contained a large number of small hyaline bodies, which were observed under the microscope to increase in size and change their form and pass through a cycle of development to what appeared to be a spore-forming stage, was injected into three animals—two, a dog and a guinea-pig, in the peritoneal cavity; one, a guinea-pig, in the jugular. The guinea-pig and dog which were inoculated in the peritoneal cavity developed no tumor-formation, but a marked peritonitis and enlargement of the regional lymph nodes. The abdominal cavities of each animal contained a small amount of fluid; and in this fluid we were able to detect the characteristic spherical bodies, nucleated bodies, and sacs filled with the granules already described as being present in the primary case.

Slides taken from this fluid and incubated for a period of three or four days in the thermostat, showed that the bodies not only changed their form, but we were able to trace the development of the larger structures from the small hyaline forms. Of particular interest was a portion of a slide so treated, in which we found numbers of the organisms which had sent out pseudopodia toward a neighboring air cell. There were at least twenty organisms so arranged, and all of them had run out long pseudopodial projections to its margin.

The animal injected in the jugular was killed after fifty days. On section, the lungs were found to contain minute white nodules, which, on microscopical examination, proved to be beginning foci of adeno-carcinoma. The pulmonary blood vessels showed marked proliferation of the epithelial and adventitial cells. The spleen of the animal contained a large amount of blood pigment, and the Malpighian corpuscles were enlarged. The cells of the

tumor and those of the enlarged follicles in the spleen are each found to contain within the nucleus, irregularly shaped deeply stained bodies of unusual appearance. About the periphery of the follicles and scattered through the splenic pulp, were a number of round and oval bodies, which corresponded morphologically to what are known as Russell's fuchsin bodies. In the perivascular lymph spaces of the lung, we have since been able to detect, by employing Plimmer's staining method, the presence of the half-grown organisms in large numbers, which correspond to those described by him as of constant occurrence in carcinoma in man.

Our attempts to cultivate these organisms at the time of this experiment were not followed by success, as the forms of culture media employed were unsuitable. As will be seen later, in the experiments which shortly followed upon this just described, we met with better success, and succeeded in cultivating with comparative regularity, directly from cancer, from fluids which were in contact with cancer and from experimental animals, the organisms which have been described in this first experiment. The medium which has thus far given us the best results is that recommended by Celli for the cultivation of amoebae, fucus crispus bouillon.

Two other animals were inoculated at this time, one a guinea-pig, in the peritoneal cavity, which was killed after nineteen days, and a dog which rapidly became emaciated and died after sixty-four days, presenting marked evidence of peritonitis with general enlargement of the regional lymph nodes, enlargement of the spleen, and oedema of the lungs. In the peritoneal fluid and the heart's blood, as well as from the organs of these animals, we were able to detect large numbers of the parasites. Sections of these organs, which have since been stained with Plimmer's method, reveal the

presence of large numbers of the parasites in all of the viscera especially numerous, however, in the lymph nodes and lungs.

A number of tubes of the serum from this first case have been retained in the Laboratory, and animals have been inoculated with them at later periods. Of special interest are guinea-pigs 40, 42 and 43, which were inoculated with this serum which had stood for four months, with no other precautions being taken than placing the tube which contained it in a cool place. The animals inoculated at this later period gave identically the same results as those of the original experiments.

During the period of these first experiments I was fortunate in having as an assistant Dr. F. C. Busch, who now occupies the chair of physiology in the University of Buffalo. Dr. Busch was of the greatest service to me, and assisted me in all of the work of that period with great skill and devotion.

Following these first experiments, our efforts were especially directed toward an investigation of the fresh scrapings of cancers, and in attempting to demonstrate these bodies in the tissue in hardened sections. Having once established the fact that the small spherical bodies which so closely resemble fat were not fat (giving no reaction with osmic acid* and not being affected by fat solvents), we set about to determine how the great discrepancy between the

*In determining the reaction of these bodies to osmic acid, fat was used as a control and placed under the same conditions. In one or two cases, after a treatment of one or two days with osmic acid, the writer has observed a slight browning of the periphery of these bodies, but fat used as a control had long before given the intense black reaction which characterizes it. We are not certain whether or not it is possible to cause browning, or possibly even blackening of these bodies by osmic acid, if treated in some special manner. This question will be the subject of a special piece of research in the Laboratory, but will in no way affect the significance of our findings. Sections hardened in Hermann's fluid, in which the fat in the tissue gives the usual black reaction, when cleared in origanum oil and covered with a coverglass without staining, show bodies that are of a yellowish color,

large number of parasites found in fresh cancer and in sections, could be accounted for.

A careful examination of a large number of tumors, including those removed by operation, shows that in all rapidly growing tumors, especially when of large size, a great number of organisms are present. Small tumors, as a rule, were found to contain only the smaller forms of the organisms; the tumors and organs removed from cadavers of patients who had died from carcinoma or sarcoma showed the presence, especially in the tumors, of great numbers of the organisms in all phases of development. After comparing tumors removed by operation and those from cadavers, it becomes evident that the organisms either increase very rapidly during the period just before death, or that they proliferate in the tissues after death. In two cases of large-sized tumors, which immediately after operation contained a predominating number of the small forms of the organism, and which were retained sterile, we were able to make the following observation:

An examination of successive scrapings from the tumor, several hours apart, in each case showed that the relative size of the organisms gradually increased. In the course of ten hours, repeated scrapings showed that the amoeboid forms were greatly increased in number; and after twenty-four hours the spore sacs of the organism were present, for the first time, in large number. Continuing our observation up to a period of about three days, we observed in these two cases that the sacs were ultimately replaced by groups of hyaline bodies, which were considerably larger than those which the sacs originally contained. It will be seen from this observation, that the so-called fatty degeneration of carcinoma is at least in some part due to the presence of the various forms of the organism which have been mistaken for fat droplets and infected

epithelial cells which were supposed to be in an advanced stage of fatty degeneration.

We were likewise able to determine that in the center of carcinomata which had undergone degeneration, the fluid, the so-called cancer-milk of the older writers, consists practically of a pure culture of these organisms. The fluid from malignant ovarian cysts likewise contains a large number of the organisms, and the peculiarly characteristic mush found in the cavities of certain adenocarcinomata of the ovaries is likewise largely composed of the various forms of the parasite.

We were thus forced to conclude that bodies identical in appearance to those observed by us in the peritoneal fluid of our first case could be found in all scrapings of cancer. The small highly refractive form which in suspension possesses a characteristic oscillating motion, the larger pale forms projecting pseudopodia, and the saccular forms containing highly refractive spherical bodies, could be detected with equal facility in the fresh scrapings of any malignant tumor. The small form of the organism which so closely resembles fat, and the larger spherical forms containing fine granules are particularly abundant. By incubating hanging drop preparations of fresh scrapings from cancer, the smaller forms can be followed in their development, during which they grow in size and finally become granulated, and, if kept upon a warm stage, ultimately throw out pseudopodia, develop a nucleus, and end by turning into a sac containing the spore forms of the organism. Owing to the fact that the specific gravity of the organism is less than water, it rises to the surface, and must be sought directly beneath the coverslip, and not in the lower portions of the fluid. This fact we had noticed and made use of before the recent publication of Funk on the vaccine organism.

Having ascertained that a large number of organisms were invariably present in cancer we undertook to determine why these organisms could not be demonstrated with the ordinary staining methods in the tissues, and were able, first of all, to determine that the application of almost all fixatives caused the disappearance of all the spore sacs of the organisms, and the greater part of the large spherical and granular bodies. Only the small, more resistant forms of the organism remained, and these we were able to stain in a large number of sections with the aniline dyes, in which case they presented the form which has already been recognized and first described by Russell, known as "Russell's fuchsin bodies." The larger forms which are still hyaline in character, or contain fine granules, and which might be spoken of as the quarter-grown organism, in sections stained by the ordinary methods so closely resembled free nuclei and round cells, that it was impossible to state which were parasites and which tissue elements. In one case, however, of carcinoma of the bladder, observed during this period, where the organisms appeared in large numbers in the urine, we were able to detect, even in haematoxylin preparations, the quarter-grown form of the parasite between the epithelial cells, and attached to the surface of the tumor after removal.

In the summer of 1898, the writer was asked to make an autopsy on a female patient who had died of carcinoma of the uterus. On opening the peritoneal cavity, we were surprised to find an advanced general peritonitis. There was considerable clear fluid in the peritoneal cavity, and the surface of the peritoneum had lost its brilliancy. The intestines were matted together, and the thought was immediately awakened, that a perforation of the vagina had probably occurred, as the cancer involved the cervix, and that bacteria had entered the peritoneal cavity and had thus produced a secondary

infection. On examining the spleen, it was found that nearly one-half of this organ was in a condition of infarction; and on examining the lungs, they were found to be markedly oedematous. Cultures for bacteria were made from the peritoneal cavity, the spleen, the blood and the lungs, with the result, which was determined later, that they all remained bacteriologically sterile.

On returning to an investigation of the pelvic organs, we were immediately struck with the fact that there was no perforation, which at once directed our attention to the possibility that the case might be one of general infection with the organism of cancer. For this reason, we immediately made fresh preparations from the surface of the peritoneum, the substance of the spleen, the lungs, the heart's blood, and one of the larger superficial veins of the lower extremity. In all of these were found large numbers of the pale hyaline forms which we had already learned to recognize as constant in scrapings from carcinoma, in the peritoneal fluid of carcinomatous patients, and in the heart's blood and peritoneal fluid of our experimental animals. Dr. Irving Phillips Lyon, associated with the laboratory, was present with me at the autopsy and confirmed my observations.

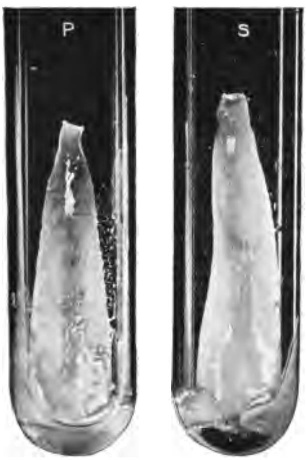
This was the status of our work in December, 1898, and it was upon the basis of these facts that the writer made the statement, before the Medical Society of the State of New York, in January, 1899, which was quoted at the beginning of this paper. It will be seen from this statement, that we believed we had recognized and demonstrated the presence of parasites in cancer and had successfully produced cancer in one animal, but that we were at that time not in a position to state what the nature of these parasites might be.

During the winter of 1898-99, the writer planned an elaborate series of experiments, based upon our original experiment, which

are only just completed. With the clew afforded by the findings of the autopsy described above, we have examined, since that time, the organs of a number of cadavers which have died from cancer, and on the basis of these observations we are prepared to state that *all the organs, including the blood taken from all regions, of all cases dying of cancer, including sarcoma and epithelioma, contain large numbers of the organisms.*

Following the same lines we have likewise observed in all cases of carcinoma and sarcoma thus far examined (four cases of general visceral carcinosis, one case of advanced cancer of the breast, one case of malignant lymphoma, one case of general sarcomatosis, which were in the last stages of the disease, in which cachexia was well marked), that the organisms, especially the younger forms, can be detected in the peripheral blood. In the first case examined for this purpose, a case of malignant lymphoma, the method which was employed was as follows: A sterile pipette attached to a sterile hypodermic needle was inserted into the median vein of the arm and 10 or 15 cc. of blood withdrawn. This was immediately placed in sterile test tubes and permitted to coagulate. The tubes were placed in the thermostat and incubated and control tubes of ordinary culture media were inoculated to exclude bacterial contamination. In the serum of the blood thus obtained were found the small, spherical, hyaline bodies, with the characteristic oscillating motion aready described. A small, sterile, capillary tube was filled with this serum and the ends sealed. Careful examinations were made from day to day. The first examinations revealed nothing but the small, hyaline forms within the tube. These gradually increased in size (see Figs. 2 and 3, Plate VI). At the end of three weeks the bodies gradually became granular and slowly sent out pseudopodia. In this stage they closely resembled the amoeboid

PLATE VII.



1.

Potato cultures of Plimmer's yeast and Sanfelice's "Saccharomyces Neoformans."

2

Fresh preparation of "Saccharomyces Neoformans," Sanfelice. (Oil immersion.)

3.

Fresh preparation of Plimmer's yeast. (Oil immersion.)

bodies found in the blood by Pfeiffer and Reed, after vaccination and in cases of smallpox, although the amoeboid motion was not as active as described by them. At the end of six weeks a large number of the organisms were found to have become transformed into the typical morula stage or spore cysts of the organism. In the remaining six cases the small hyaline forms of the organism were detected and in one case (general carcinosis) small, amoeboid bodies were found in the blood immediately after it was withdrawn from the patient. These conformed very closely in appearance to similar bodies described by Pfeiffer and Reed in the blood of vaccinated children and monkeys. The significence of the presence of the organisms in the peripheral blood and the time of their appearance will form the subject of a piece of special research in the laboratory. The younger forms of the organism may likewise be found in the peripheral blood of the animals after inoculation with cultures or carcinomatous material.*

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*As the editorial comment upon the above paragraph, as it appeared in *The American Journal of the Medical Sciences*, shows evident misinterpretation of the writer's meaning, he has deemed it advisable to give the wording a more specific character. He has carefully avoided any theoretical deductions and has merely recorded observations as they were made in the laboratory, with the intention of describing all of the experiments in detail in future publications. One evident misinterpretation credits the writer with the belief that cancer is a general and not a local disease. He trusts that those who will reread that portion of the article as it appeared in the *American Journal* will see that no deduction of this sort is warrantable. Cancer unquestionably begins as a local infection of the epithelium, and at some stage of the disease, yet undetermined, the organisms apparently find their way into the general circulation, and as stated above, after death can be found in all of the organs of the cadaver. The exact role which the organisms play when in the peripheral blood is naturally undetermined. It is even fair to assume, from what is known of similar organisms, that they are entirely passive. A number of the protozoa which infect the blood of the lower animals produce very slight disturbance, and it is highly probable that the significance in this case is of no greater importance than showing the general distribution of the parasites in the later stages of the disease. It is our belief that the termination of fatal cancer cases bears some relation to the general distribution of the organisms, but we have carefully avoided all speculations as to the significance of the above observations.

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Having reported before the State Society our findings of parasites in cancer, it remained for us to determine the nature of these organisms and to continue our investigation in the most comprehensive manner possible. It became at once apparent, that there could be but two possibilities in the case—either that the organisms were of an animal nature, and were then protozoa, or that they belonged in the vegetable kingdom, in which case they were, in all probability, low forms of fungi, probably yeasts. In order to understand the difficulties which prevented our arriving at an immediate conclusion as to the nature of these parasites, it is well to review the status of scientific research at that time.

When, in 1898, the State of New York established a laboratory for the investigation of cancer, the attention of the scientific world was attracted by a series of five articles published by an Italian investigator, Sanfelice, of Cagliari, Sardinia, all of which appeared in the *Zeitschrift für Hygiene und Infectionskrankheiten.* Besides these, a number of articles appeared in different periodicals by a second Italian investigator, Roncali. These last are of less importance. The purport of the articles of both of these investigators, was that the parasitic inclusions found in cancer were identical in appearance with yeast organisms or blastomycetes when injected into the tissues of animals. Sanfelice's articles went further, and in the twenty-ninth volume, 1898, of the above mentioned journal, he published an account of tumors which he succeeded in producing by inoculation with a yeast in two dogs, both of which he wishes to designate as true adeno-carcinoma forming metastases.

Before entering into a discussion of the merits of Sanfelice's investigations, it is well to state that the first observer to interpret the spherical, hyaline bodies found in cancer as blastomycetes, was Russell. Russell published an article in the British Medical

Journal,* in 1890, in which he claimed that he had detected micro-organisms to which he gave the non-committal name of "fuchsin body." These were found in groups or clusters of from two or three to twenty or more. They were from four to twelve microns in diameter, were apparently homogeneous, and in some cases the groups of bodies were held together by a faintly stained material. He believed they belonged in the yeast group (Sprosspilze). Russell made no attempts to cultivate these organisms. His publication led to very heated discussion, and his work was attacked, especially by Shattuck and Ballance (*British Medical Journal, Vol. I, p. 565, 1890*), and Klein (*Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie, Bd. XI, 1891*). The first of these authors described similar bodies found in caseating lymph nodes and the walls of senile arteries, while Klein was of the opinion that Russell's bodies bore a close relation to Altmann's cell granulae.

In 1895, Busse, a German investigator, published the first description of an undoubted yeast, which he found to be the cause of a fatal infection in man. This organism he succeeded in isolating in pure culture, and found that the lesions which it produced were a combination of abscess and tumor formation. Ueber saccharomycosis hominis (*Virchow's Archiv., Vol. 140, page 23*). The appearance of the organisms in the tissue was so suggestive of the cell inclusions in carcinoma, that Busse had previously published a description of the case under the title, "On parasitic cell inclusions and their cultivation," in the *Centralblatt für Bacteriologie, Vol. XVI*. These organisms were very common within the large cells which composed the walls of the abscess cavities, and under these conditions presented an appearance very much

*An address on A Characteristic Organism of Cancer, Vol. II, p. 1356, Dec. 13, 1890.

like the cell inclusions of carcinoma. In 1897, Busse published a monograph entitled "The yeast organism as the cause of disease." In his last publication, he is distinctly of the opinion that the pathogenic yeasts and the cell inclusions in cancer have no relation to each other. He describes a series of experiments which he carried out in the hope of causing proliferation of the cell inclusions of cancer. For this purpose he planted small portions of tumor in which he had detected the inclusions in various kinds of culture media, and placed them for several days in a thermostat. In none of these experiments was he able either to obtain a culture of organisms or to observe that the cell inclusions showed any evidence of increase in number or change of form. He likewise attempted to inoculate animals with small portions of lympho-sarcoma, with negative results. He included a short description of all of the organisms of the same class described up to the time of his publication, and, because of the negative results obtained, and the fact that no positive evidence had been produced to show the identity of cell inclusions and yeast organisms, he concluded that they had nothing to do with each other, and that the yeast organism played no role in the production of carcinoma. Besides Busse, a number of observers have since described lesions of various kinds (especially skin lesions) produced by yeast organisms.*

The articles of Sanfelice are of the greatest interest, as he has undertaken to elucidate the subject by a careful study of wild yeasts and such as he found to possess pathogenic properties for animals. Among these was one obtained by cultivation from the skin of a lemon, which, when injected into animals, produced granulomata. These, in his opinion, closely resembled sarcoma,

*Gilchrist, *Johns Hopkins Hospital Reports, Vol. I.;* Gilchrist and Stokes, *Journal of Experimental Medicine*, 1898; L. Hektoen, *Journal of Experimental Medicine, Vol. IV, p. 261.*

for which reason he gave the organism the name "saccharomyces neoformans." In 1898, Sanfelice published an account in which he stated that in his experiments he had inoculated, up to 1896, fifty-nine dogs. His method of inoculation he had varied as much as possible—some in the subcutaneous connective tissue, others in the testes, others in the breast, the spleen, the liver, the lungs, the jugular vein, and the peritoneum. Most of the animals showed no pathological change and were killed after three, four and five months. In the greater number of these animals, Sanfelice was unable to cultivate the organisms from the region of the inoculation, but in most cases he was able to secure them from the regional lymph nodes. By transferring his organism from dog to dog, he succeeded in increasing its virulence to such an extent that, while, in the beginning, when injected into the jugular vein, it produced no lesions, in the end similar inoculations resulted in the death of the animal, with the develoment of characteristic changes in various organs. Besides simple inoculations, he practised various methods to reduce the resistance of the animals, such as drawing a portion of their blood, injuring the tissues before inoculation, and introducing foreign bodies at the time of the inoculation. None of these devices produced any further results than those obtained by the simple inoculation. He ultimately succeeded in obtaining what he described as a positive result, by inoculating a female dog with a culture of saccharomyces neoformans which had passed through a large number of dogs. A small portion of the culture was removed with a platinum needle, emulsified with sterile water and injected into the breast with an ordinary sterile syringe. After the first few days, the breast showed a certain amount of swelling and inflammatory reaction. This disappeared after a few days, and the breast presented a normal appearance.

After several months, he observed that the breast, in the neighborhood of the inoculation, began to swell, and this increased gradually until a definite tumor was formed, which at the time of the death of the dog, ten months later, was about half the size of an egg. With the development of the tumor, the dog showed definite signs of emaciation. The tumor was of greater consistence than the breast, and the nipple was retracted. The skin in one or two places was apparently adherent to the tumor. The inguinal lymph nodes on both sides were somewhat enlarged, the largest about the size of an almond; the smallest, the size of a hazelnut. The organs of the thorax and head showed no pathological changes.

Microscopical sections made through the tumor showed that the center of the structure did not possess the same histological characteristics as the periphery. At the center the tumor presented the appearance of the normal breast of the dog. At the periphery the histological characteristics of the tumor were such, to judge from the description of the author, as strongly to suggest malignant change. Instead of the single layer of epithelium lining the spaces in the connective tissue stroma, which characterized the center of the tumor, the portions near the periphery were lined by multiple layers of large epithelial cells. The nuclei were irregularly arranged, of varying size and form, and the membrana propria of the canals was missing. Isolated nests of epithelium were likewise to be found in the stroma. The epithelium exceeded in amount the connective tissue stroma. Sanfelice found that the enlarged lymph nodes on section presented the appearance of containing metastatic deposits of the large tumor. Sections cut from these lymph nodes showed that they actually contained epithelial structures of similar form and appearance to the peripheral portions of the tumor.

From the description of the tumor given, indicating the development of metastases in the regional lymph nodes, if the description of the author can be taken, there is little reason to suppose that the case was not one of true adeno-carcinoma. *From the original tumor and all of the lymph nodes, Sanfelice was unable to obtain cultures of his organism, and neither in the metastatic deposits nor in the primary tumor was he able to demonstrate bodies which were unquestionably yeasts.*

Besides the case just mentioned, Sanfelice describes a second dog, which was inoculated in the testicles, and which, after a period of four months, had developed a well defined enlargement of the organ and several nodular masses, which appeared to be enlarged regional nodes. Several nodular masses were found within the prepuce of the animal, and Sanfelice observed that from the orifice a small amount of purulent fluid could be expressed, in the cells of which he detected inclusions closely resembling the bodies of Russell, which he considered to be altered yeasts.

The animal died unexpectedly during the sixth month; and at the autopsy, which was performed with the assistance of Prof. Charbone (pathologist), the nodular enlargement of the testicle was found to be of yellowish-white appearance, of definite consistence, which could not be sharply differentiated from the tissue of the testicle. On both sides of the penis bone were a large number of apparently metastatic deposits, one of these as large as a hazelnut, the majority about the size of peas. Surrounding the glans was a conical mass of newly formed tissue, which communicated with the preputial opening. The primary tumor appeared to be in the testicle, and the smaller deposits appeared to be of a metastatic nature. The inguinal lymph nodes were slightly enlarged, and on

section presented a normal appearance. The spleen, kidneys and liver were slightly hyperaemic, but showed no other changes.

As the autopsy revealed no well defined cause for the exitus, the decision was reached that the animal had been surreptitiously poisoned. Cultures which were made by emulsifying portions of the tumor and metastases were all negative. Portions of the tumor were used to inoculate other animals. At the time of the publication, Sanfelice was not in a position to state the outcome of these experiments. Sections of the tumor showed it to be very probably of epithelial nature. The cells of the tumor were rather small, and closely resembled those of the basal cells of the seminal vesicles of the dog.

In 1898 the writer had the pleasure of making Professor Sanfelice's acquaintance and carefully going over with him the sections from these two cases and obtaining from him a culture of the saccharomyces neoformans and blocks of tissue from the two tumors. It is important in estimating the work of an observer to know something of his character and temperament, and for that reason it was a great pleasure to make Prof. Sanfelice's acquaintance. He is a man of unquestionable sincerity and honor, and no matter what the interpretation of the work which he has published may be, his statements can be accepted as accurate so far as observation can make them. There is absolutely no question that the tumor of the breast with metastases in the regional lymph nodes, described by Sanfelice, would pass muster as an adeno-carcinoma.*

The courtesy which Prof. Sanfelice showed me in placing before me and at my disposal, all of his material, has been of the greatest service to the Laboratory, and I wish to take this occasion to publicly thank him for it. The culture which he forwarded to us was

*The probable significance of these experiments will be considered in Part 2 of this article.

that of an ordinary yeast, so far as we are able to classify it. The appearance of the culture and of the fresh organism is shown in Plate VII, Figs. 1 and 2.

The publications of Roncali have been confined to the description of attempts to cultivate yeasts from carcinomata. He describes several successful attempts in which he employed acid sugar water as the medium. The writer was not deeply impressed with the preparations which Prof. Roncali showed him, and, as his cultivation experiments are so widely at variance with those of other observers and ourselves, we feel that they do not require a detailed description.

In the April number of the Practitioner, '99, there appeared an article by Plimmer, which is without doubt the most important communication in a number of that journal devoted entirely to the subject of cancer. After a short review of the literature, and an analytical discussion of the structure of cancer, Plimmer gives the method by which he has examined a large number of cancers of various types. He recommends various hardening and staining methods for the demonstration of cellular inclusions, and, as in our experience one of these methods gives pre-eminent results, it would seem desirable to introduce it at this point:

1. Small slices of tissue are hardened in Hermann's fluid 12 to 24 hours.

2. Thorough washing in running water, 12 to 24 hours.

3. Harden in alcohol. Embed in paraffine.

4. Remove paraffine in xylol.

5. Absolute alcohol.

6. Place in peroxide of hydrogen until the black is removed from the section and no further bubbles form upon the surface. One quarter to half an hour.

7. Wash in water.

8. Stain with Haidenhain's iron haematoxylin or Mallory's simple iron haematoxylin.

9. Thorough washing in running water 3 to 6 hours.

10. Stain in one per cent. Ehrlich's neutral red or Bordeaux red. (This solution must be kept neutral. When it becomes acid it must be neutralized with alkali.) After staining with iron haematoxylin, the differentiation must be continued until the protoplasm is colorless. The amount of red in the preparation must be controlled under the microscope.

Parasitic bodies in cancer and yeast organisms in the tissue are stained yellowish red to coppery red; nuclei, blue black; connective tissue structures, brilliant red.

Plimmer's description of the bodies is as follows:

"The parasites, as they most often occur, are round bodies of very diverse sizes, from .004 mm. to .04 mm., or even more, in diameter. There is a central portion, which I shall call here, for convenience, the nucleus, although there is nothing in this central portion in common with the biological nucleus, which is generally round, but which may be irregular in shape; around the nucleus is a layer of protoplasm, and outside this is a capsule. This nucleus differs in its micro-chemical reactions from the nucleus of the cell; it takes, with the Ehrlich-Biondi solution, a copper-red color; with thionin, a dark purple; and with (1) of the double haematoxylin stains, described on page 440, it also takes a copper-red color, quite different from the red of either the protoplasm or the fibrous stroma; and with (2) it takes a dark claret color, again darker than that of the protoplasm or stroma. With the Ehrlich-Biondi stain, it reacts somewhat like the nucleolus of the cancer-cell nucleus, but the color of the latter is much brighter; moreover, with many other

stains—such as anilin blue, or *bleu de Lyon*, anilin green—it does not, as does the nucleolus, lose the stain when washed with spirit, but retains it even after immersion. This is to be remembered against the assertion that these bodies are aberrant nuclear structures. In very perfectly fixed specimens a lighter spot can be observed in the nucleus, which is not visible in fresh specimens; but in fresh specimens the nucleus appears to be larger than in fixed ones. It is to be noted that the nucleus is practically refractory to haematoxylin used in the strongest manner possible, when this is done by the ordinary methods. This, again, is very important in connection with the statement that the bodies are nuclear structures.

"The layer of protoplasm around the nucleus is generally homogeneous, and stains much less deeply than the nucleus. With alcohol fixation, again, the phenomenon of metachromatism is sometimes seen, the protoplasm staining blue with the Ehrlich-Biondi mixture. When the parasite has attained a certain size, a rayed appearance is often seen in the protoplasm, but I have never seen this in the fresh state, and think it may be due to the fixative.

"The capsule is a very well marked structure, which can be seen well, both in the fresh as well as in fixed specimens. That this capsule is a part of the parasite can be demonstrated by the fact that it can sometimes be seen folded over on itself, and sometimes from fixation it shrinks away from the protoplasm of the cell, and also the parasite can sometimes be seen free in an alveolus with its capsule around it. It stains more definitely than either the nucleus or protoplasm; with the Ehrlich-Biondi mixture it is a brighter red than either of the other structures; with thionin it is darker; with haematoxylin, acid fuchsin, and orange, it is a clear bright red; and with haematoxylin and Bordeaux red, it shows best as a very bright red line.

"This description applies to the forms most commonly met with, but there are some other forms which are met with, especially in cancers of rapid growth; they are, however, rare, so I will merely tabulate them:

"(1) The form described above, in which the nucleus has attached to it a small body with similar reactions, i. e., reproduction by budding.

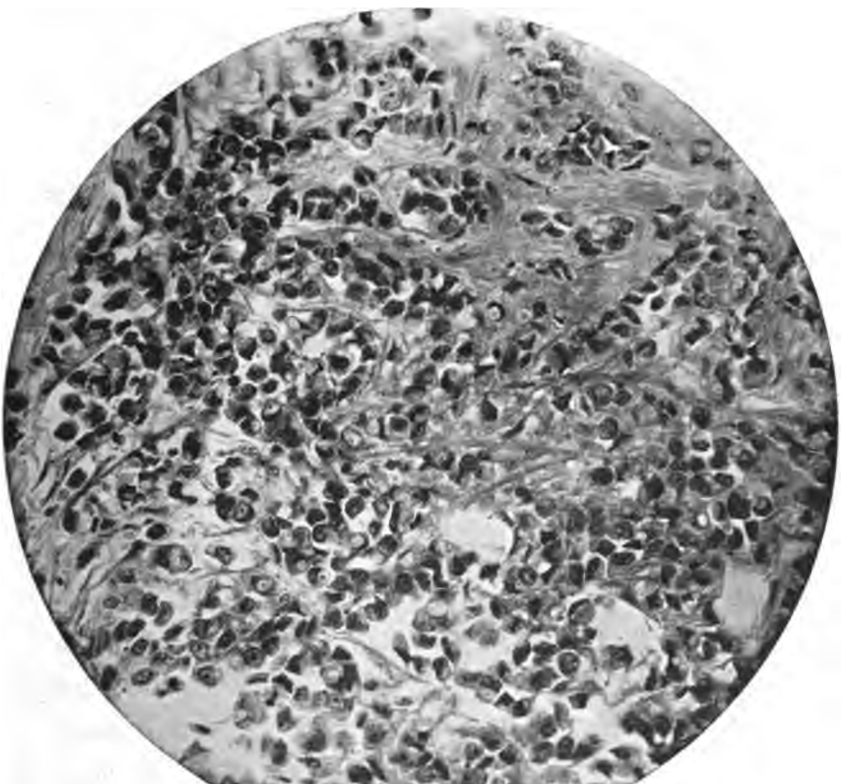
"(2) A very small form, consisting of a capsule with a small central dot, staining similarly to the nucleus of the larger forms.

"(3) A larger form, consisting of a capsule in which are two large dots in one diameter, and two smaller dots in another diameter at right angles to the first.

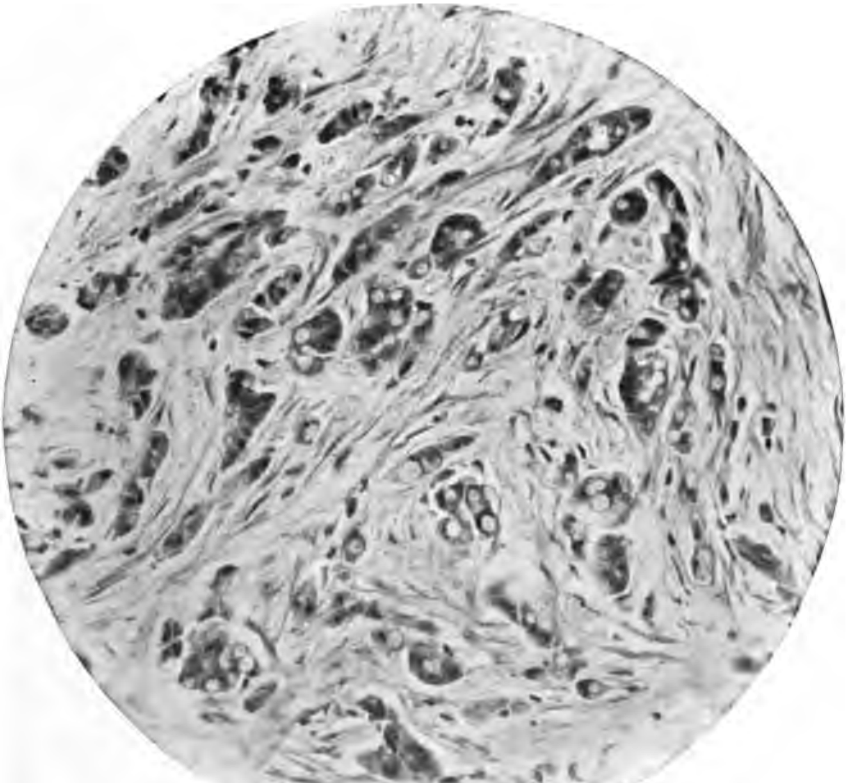
"(4) A larger form again, consisting of a fine capsule, in which are a number of fine dots, not arranged systematically.

"(5) A still larger form, consisting of a well-marked capsule, in which is a central nucleus with generally six smaller dots arranged around it."

Plimmer states that during a period of six years he has examined microscopically 1,278 cancers. These did not include any cases of sarcoma. In 1,130 of these cases he found parasitic bodies which come under the heading of those just described by him. His list included cancer of the breast, skin, including tongue and penis, uterus and vagina, stomach and intestines, liver, pancreas, lung, bladder and glands. The parasites were not found in all portions of the cancer, but were usually present at the growing edge, and in the degenerated portions of the growths they were absent. They appear only in the bodies of active cells, and not in those which show retrograde or degenerative changes. They may be found free lying between the cells and having the same reactions as those which are included within the cell protoplasm. They may also be found in leucocytes. They did not appear in anything like equal



Section of rapidly growing carcinoma of breast. (Original preparation from Plimmer stained with Plimmer's method.) Nearly every cell contains a Plimmer body (inter-cellular protozoa). (Low Power.)



Section of rapidly growing carcinoma of breast. (Case 113, Buffalo.) The magnification is the same as Plate VIII. Nearly every cell contains a parasite. Many cells contain more than one.

numbers in all cases. Generally speaking, in most cancers, they were compartively few in number, but in some very rapidly growing cancers they could be found in enormous numbers, as in the case which he illustrates. He states that in his entire list he has only nine in which there were a large number of parasites; but in these cases there was scarcely a cell which did not contain one or more, or even as many as sixty, parasites. He states that he has likewise examined a large number of other pathological conditions with a view of determining whether similar bodies could be found. These structures included gummata, histioid tumors of all kinds, tubercular growths, glanders, actinomycotic growths and tissues which had been irritated, as well as normal tissues, and concludes by stating, "I have never in man, in any instance, seen any intra- or extra-cellular bodies which were like the parasitic bodies described above, or which had their reactions."

The sixth portion of Plimmer's article is devoted to a description of attempts to cultivate the parasitic inclusions which he describes, and states that in the last case which he has investigated, and which contains a large number of parasitic bodies, he was able to isolate the organism which, in certain animals, was capable of causing death by the production of tumors in various parts. The primary growth was a carcinoma of the breast taken from a woman aged 35 years. It had a history of only two months' duration, and was growing rapidly at the time of operation. Prof. Plimmer has been kind enough to present me a section from this case, a photograph of which is shown on Plate VIII. In cultivating the organism, he employed a medium, the basis of which was an infusion of cancer prepared according to the formula employed for ordinary bouillon, and to this was added, after careful neutralization, two per cent. of glucose and one per cent. of tartaric acid. Into this were introduced small pieces of the

growth, cut with all possible precaution against contamination, and the inoculated tubes were placed under anaerobic conditions. After three to five days, in three of the flasks inoculated, he found a culture of an organism which undoubtedly belongs in the yeast group. We are again indebted to Professor Plimmer for a culture of this organism. When grown upon ordinary culture media, it is that of an ordinary yeast (see Plate VII, Fig. 1), and its histological characteristics are shown in Plate VII, Fig. 3.

I wish to thank Professor Plimmer for the courtesy which he has constantly shown our institution, both by communicating to us the result of his more recent work, and by supplying us with sections and cultures.

Besides Plimmer, several observers claim to have been successful in the cultivation of yeast organisms from cancer. Kahane obtained a culture of blastomyces from a cancer of the uterus; Mafucci and Sirleo have obtained cultures from malignant tumors, but their results were mostly negative; Corselli and Frisco report a case of sarcoma of the mesenteric glands, from which they isolated a blastomycis. They obtained the organism during the life of the patient, and after death from the fluid in the abdominal and thoracic cavities. This is apparently a case of true yeast infection. Curtis has reported a case of myxomatous tumor in man, from which he obtained a culture of a blastomycis, which after inoculation produced a similar tumor in a rabbit. Sawtschenko, who published an article in the Bibliotheca Medica, '95, on Sporozoa in Tumors, states that, on a further consideration of his specimens, he is now inclined to believe that they are altered yeast organisms. Anna Steckson, in an article on the blastomycis of Curtis and its relation to the etiology of tumors, Stockholm, 1900, states that she has cultivated blastomycetae from five cases of carcinoma. The organisms grew on all the ordinary forms of culture media.

In reviewing Plimmer's work, the following points present themselves:

1. Can the bodies differentiated by Plimmer's methods and found by him in a large number of cancers, be demonstrated in all cases of carcinoma?

2. Is their morphology constant and do they present characteristics by which they can be invariably recognized?

3. Can they be explained as changes in the protoplasm due to degeneration or other causes?

4. Are there morphological and biological grounds for believing that they are altered blastomycetae?

5. Do they bear any relation to the parasites described by other authors, i. e., Russell's bodies and the various cell inclusions interpreted as protozoa?

To determine whether Plimmer's bodies are constant in all malignant tumors, a systematic investigation was undertaken immediately after the publication of Plimmer's article. The writer obtained from Professor Plimmer sections from the case he had published, in which the organisms were stained, which were used for comparison, and a detailed account of his staining method was obtained in person. It will be noted in referring to Professor Plimmer's article, that he failed to mention in the description of his method for the demonstration of the bodies, the peroxide treatment of the sections which is step 6 of the method. This is an extremely important point, and may have led to negative results with those who have adhered strictly to the method as published in the Practitioner. We do not know how Plimmer came to overlook this step in his publication, or how important he regarded it, but in our experience it seems to be distinctly fundamental, as the tissues do not take either the iron haematoxylin or the red satisfactorily when it is omitted.

During the past two years, a large number of tumors, both malignant and non-malignant, as well as tissues not related to tumors, have been hardened and stained according to Plimmer's methods, and a large number of sections from each case have been carefully scrutinized. The results of our observations completely substantiate Plimmer's claim that these bodies are present in all carcinomata.

In tabulating the results we have used the terms "present," and "absent," and under "present" have classified the number of bodies encountered as "few," and "occasional." Under "few" is meant only one or two organisms to a section, or less than one organism to a section. "Occasional" means 8 or 10, or more, to a section. The results of our investigation in this direction are shown by the accompanying table:

Typical Plimmer's Bodies, Internuclear Protozoan Forms and Russell's Bodies.

	Present.		
	Few.	Occasional.	Absent.
Soft carcinoma of breast, primary, skin unbroken	8	5	....
Adeno-carcinoma of breast, primary, skin unbroken	1	....	....
Soft carcinoma of breast, with metastases in axillary lymph nodes	2	1	....
Recurrent soft carcinoma of the breast	....	2	....
Ulcerating scirrhus carcinoma of breast	1	....	....
Large fungating carcinoma of breast	....	1	....
Rapidly growing primary soft carcinoma of breast contained Plimmer's bodies in great number. Nearly every cell contained one or more well-defined bodies except in the central degenerated portions of the tumor. See Plate IX	....	1	....
Scirrhus carcinoma of the breast, material from which was not fresh.	....	....	1
Carcinoma of stomach	....	1	....
Carcinoma of stomach, metastases in liver	1	....	....
Carcinoma of stomach, metastases in mesenteric lymph nodes	....	1	....
Carcinoma of pylorus	1	....	....
Carcinoma of pylorus, metastases in mesenteric and omental lymph nodes	....	1	....
Adeno-carcinoma of rectum, with metastases	....	1	....
Adeno-carcinoma of colon	1	....	....
Adeno-carcinoma of appendix, with mucoid involvement of peritoneum. In undegenerated portions of tumor	1	....	....
Mucoid carcinoma of caecum, involving peritoneum. In undegenerate portions of tumor	1	....	....
Adeno-carcinoma of caecum	1	....	....
Carcinoma of gall-bladder	2	....	....
Secondary carcinoma of liver, ox, only organ examined	1	....	....
Carcinoma of omentum	1	....	....
Adeno-carcinoma of uterus	1	....	....
Solid soft carcinoma of uterus	....	1	....
Adeno-carcinoma of ovary	2	1	....
Adeno-carcinoma of ovary. Protozoan forms in large numbers. See Plates XI and XII	1	....	....
Case of general carcinosis, involving liver, lung, heart and kidneys, a very acute case	1	....	....
Primary adeno-carcinoma of kidney, pig	1	....	....
Hyper-nephroma from man	1	....	....

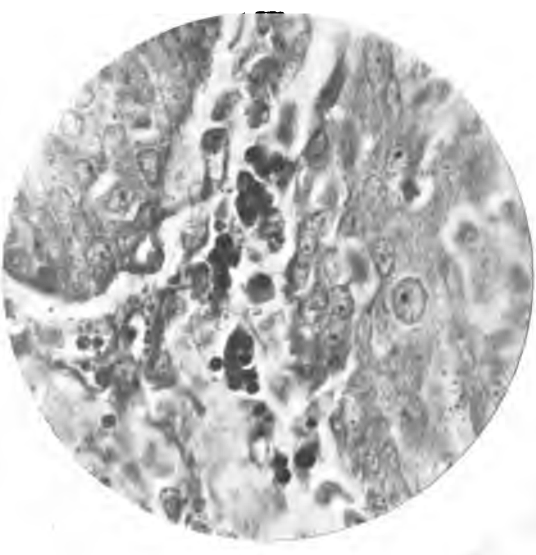
Russell's bodies from carcinomatous lymph node.
(Oil immersion.)
(Plimmer's method.)

1.

Russell's bodies from enlarged regional lymph node. (Carcinoma of breast.) (This node was used to inoculate Dog 18.)
(Oil immersion.)
(Plimmer's method.)

2.

Groups of Russell's bodies from margin of an epithelioma of skin.
(Oil immersion.)
(Methylene blue.)



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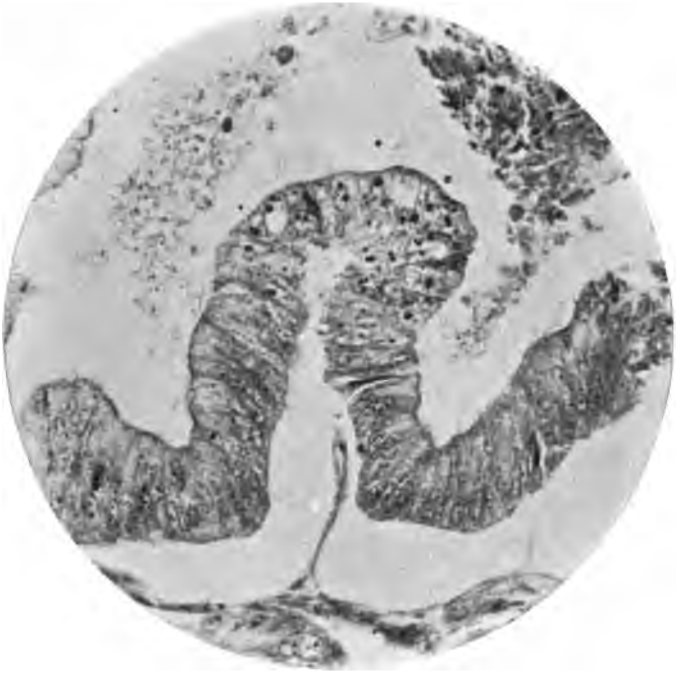
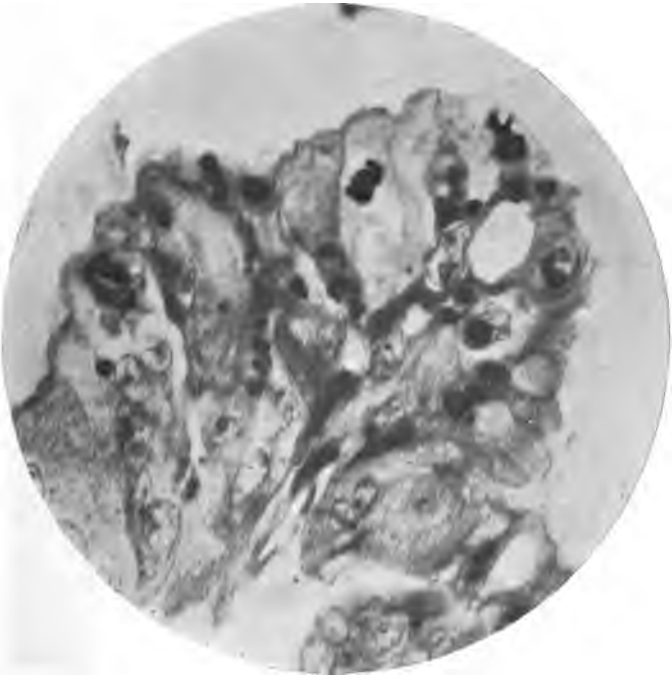


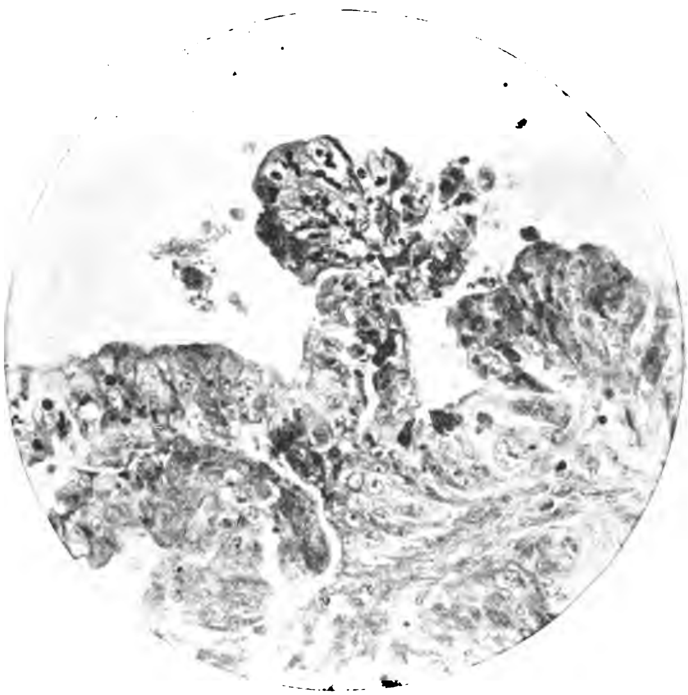
1.

Adeno carcinoma of ovary. Localization of young parasites (Russell's bodies) in the apices of the papillæ. (Plimmer's method.) (M. P.)



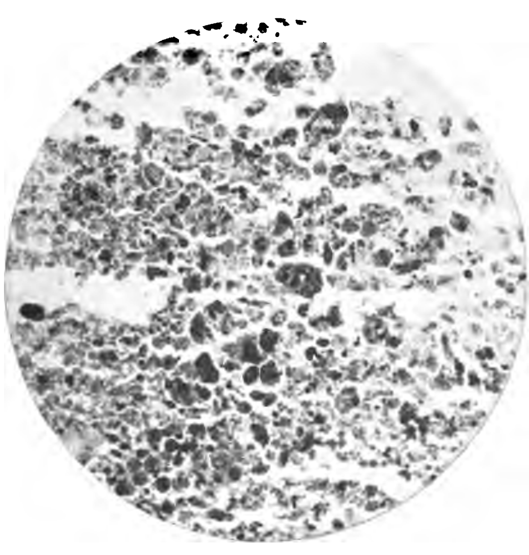
2.

Parasites with pseudopods extended. Same tumor. (Oil immersion.)



1.

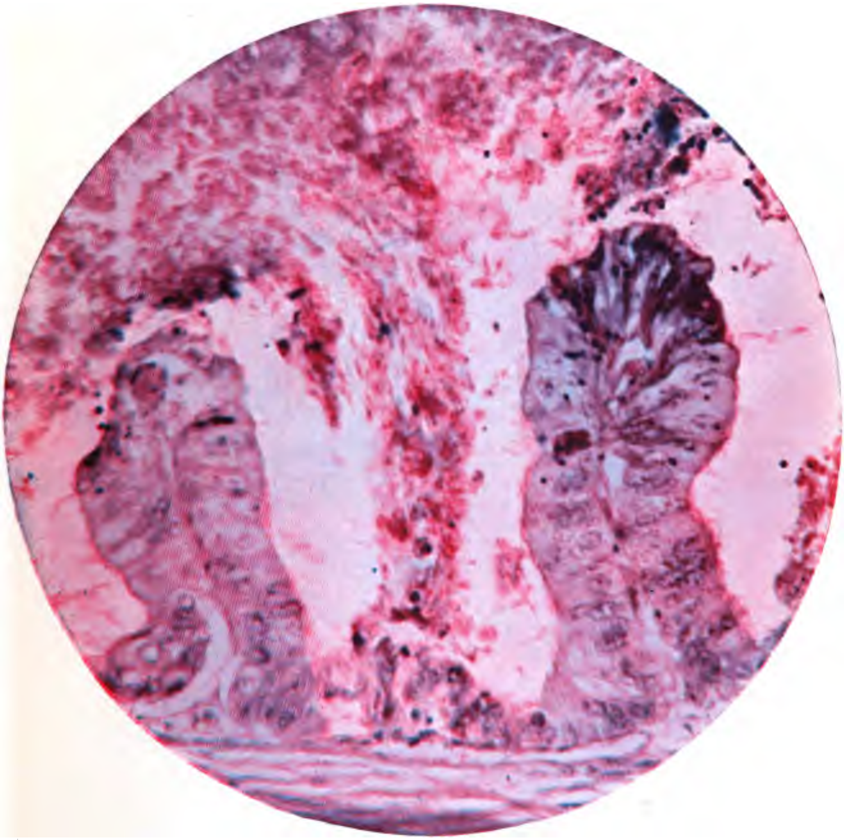
Adenocarcinoma of ovary with inter-cellular parasites. (M. P.) (Plimmer's method.)



2.

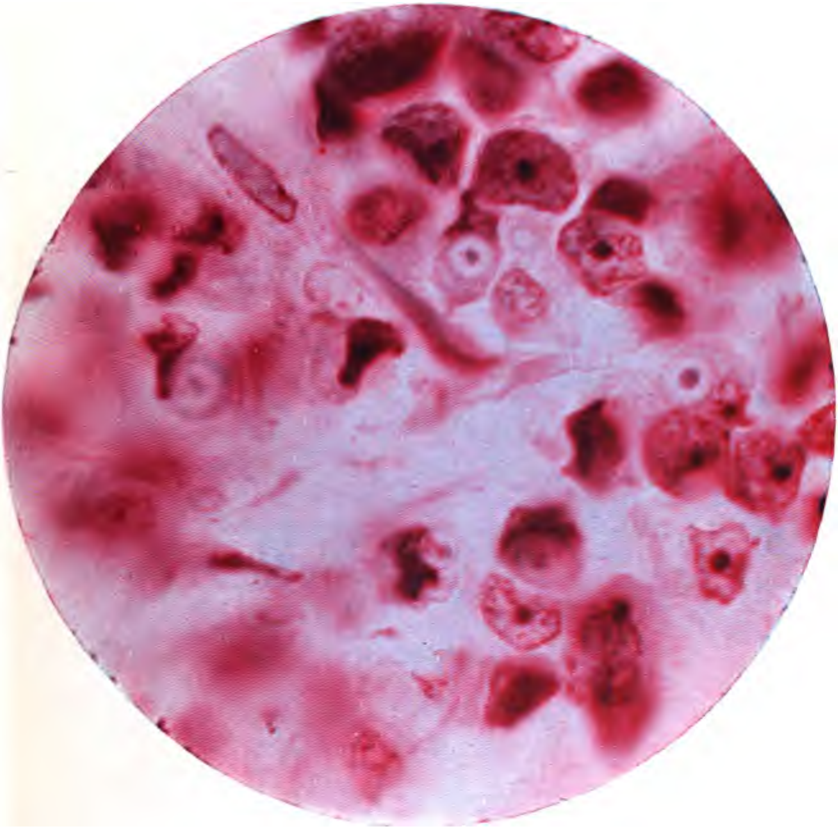
Free parasites in cystic cavity of tumor. (M. P.) (Plimmer's method.)

PLATE XIII.



Adenocarcinoma with young parasites. (Parasites blue. Plimmer's method.)

PLATE XIV.



Rapidly growing Carcinoma of breast. Plimmer's bodies.

Russell's bodies, modified Plimmer's bodies, protozoan forms.

	Present.		
	Few.	Occasional.	Absent.
Squamous epithelioma of skin	....	1	....
Squamous epithelioma of cheek	....	3	....
Squamous epithelioma of lip	....	3	....
Squamous epithelioma of tongue	....	2	....
Squamous epithelioma of penis	....	1	....
Squamous epithelioma of cervix	....	2	....
Squamous epithelioma of vagina	....	1	....
Squamous epithelioma of orbit, cow. A few atypical bodies, giving the reaction of Plimmer bodies, but much larger. See Plate XV, Fig. 1	1	....	....
Multiple sarcoma of skin	1	....	....
Melano-sarcoma of skin	3	....	....
Large spindle-celled sarcoma	1	....	....
Spindle-celled sarcoma, metastases in myocardium, horse	1	....	....
Sarcoma of kidney, rooster	1	....	....
Recurrent sarcoma of thigh	1	....	....
Sarcoma of breast	1	....	....
Sarcoma, involving thoracic wall, dog	1	....	....
Angio-sarcoma of brain	1	....	....
Round-celled sarcoma of ilium	1	....	....
Malignant lymphoma	1	....	....
Slowly developing lymphoma	1	....	....
Myxoma of breast	1	....	....
Myxoma, from pylorus of tiger shark (Galeocerdo Tigrinus)	1	....	....
Osteo-sarcoma	1	....	....
Osteo-sarcoma of jaw, horse	1	....	....
Adeno-fibroma of breast, rapidly growing, both breasts involved (see text)	1	....	....
Lipoma of abdominal wall	....	....	1
Fibroma from side of sucker (Chasmistes)	....	....	1
Fibroma of musculo-spiral nerve	....	....	1
Colloid struma	....	2	....
Tuberculosis of breast	....	....	1
Chronic cystic mastitis	....	....	1
Syphilitic lymph nodes	....	1	....

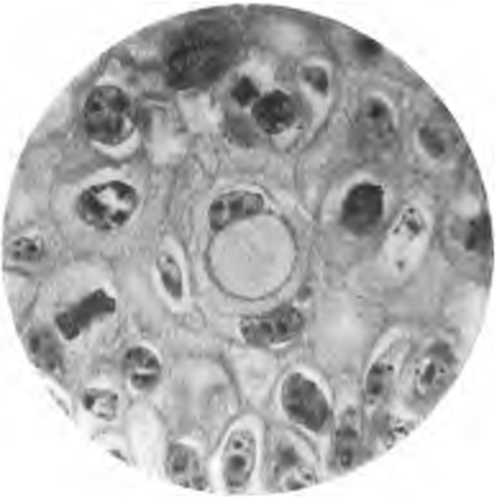
In examining the above table, it will be seen that in all cases of carcinoma investigated by this method, with the exception of one which was not fresh, Plimmer's bodies were uniformly present. Likewise, in all of these tumors, Russell's bodies were numerous, especially about the peripheries of the tumors and in the *adjacent lymph nodes, even when these contained no epithelial deposits.* Such groups of Russell's bodies are shown on Plate X. One tumor, an adeno-carcinoma of the ovary, besides containing typical Plimmer's bodies, contains a large number of cellular inclusions resembling Russell's bodies, and many larger forms which show evidence of previous amoeboid movement. These are the so-called protozoan forms of the earlier writers. It will be noted on Plate XI, Figs. 1 and 2 and Plate XII, Fig. 1, that these organisms have infected the epithelium at various points, and as a result of the

infection a proliferation has occurred which has thrown the epithelium into folds giving the characteristic papillary appearance of such tumors. As a result it is to be noted that the parasites are present in greatest number at the apices of the pipillary projections. The fluid in the cavity of this tumor appears to be nearly a pure culture of organisms. (Plate XII, Fig. 2.) This tumor was hardened immediately after the operation in sublimate, and was brought by the writer from Dresden, where it was obtained over three years ago. One of the cases in which Plimmer's bodies were found was a rapidly growing adeno-fibroma of the breast. *This case presented no histological evidence of malignancy, but occasional Plimmer bodies were found lying in the stroma and between the cells of the acini, as well as a few in cells.* They were few in number. *The patient developed a similar growth in the remaining breast, which was likewise operated upon after it had reached a large size, and it likewise contained a few Plimmer bodies.*

Besides these cases of carcinoma, 14 cases of squamous epithelioma were examined, and all of these contained *atypical bodies, which gave the staining reactions of Plimmer bodies, but were much larger and did not contain the characteristic central bodies.* The appearance of the cell inclusions from one of these cases is shown in Plate XV, Fig 1. The remainder of the list contains 15 cases of sarcoma, 11 from man and 4 from animals, *all of which contained the small forms of the organism within the nuclei. Plimmer's bodies are rare, and not so well defined as in carcinoma.*

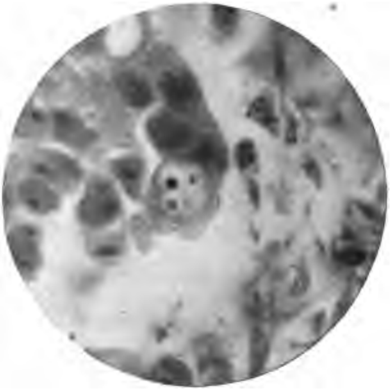
In comparing our findings with those of Plimmer, it will be seen that the results obtained by us completely substantiate his claim that typical bodies of the nature which he has described are of practically constant occurrence in carcinoma and sarcoma. Our list is not nearly so large as Plimmer's, as we have devoted our prin-

PLATE XV.



1.

2.



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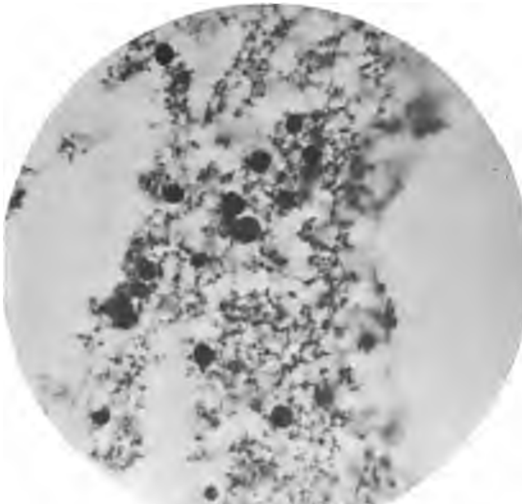


4.

cipal efforts to the experimental side of the problem, and simply wished to confirm or disprove Plimmer's results. We have not considered it necessary to examine a greater number of tumors than those employed for experimental purposes. Besides the tumors enumerated in this list, we have examined a large number fresh, and have been able invariably to demonstrate the parasites in the fresh condition.

The recognition of the nature of these bodies and the demonstration of their presence in 88 per cent. of 1,278 cases, is a feat so colossal that it places beyond any question of doubt the significance of these bodies in the cancerous process. Not only should the credit of this performance be freely accorded to Plimmer, but we must also state that the acquisition of his staining method has thrown an entirely new light upon the animal experiments which we shall describe later, and has been one of the most important factors in elucidating the entire problem.

As to whether the morphology of these structures is sufficiently constant to enable their ready recognition, the following can be stated:

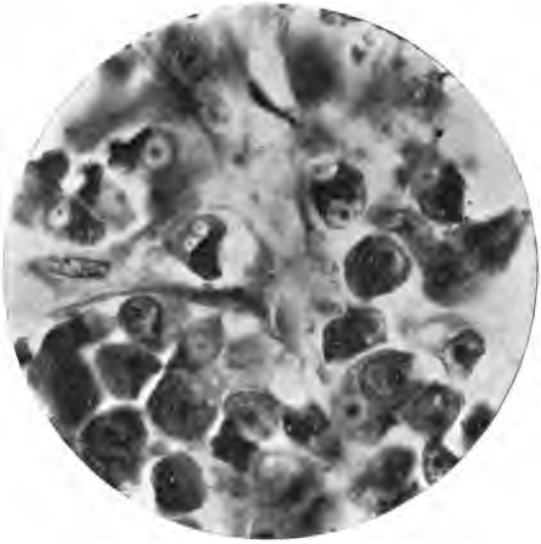
The bodies may be demonstrated in the fresh state, in which case it is a matter of considerable difficulty to distinguish them from fat droplets, which they somewhat resemble, but which have a higher refractive index and do not contain a central structure. The most minute form of the organism might be confused with cocci. In the fresh state the quarter and half grown forms appear either as spherical bodies with very delicate outlines, and containing one or two colorless granules near the center, or as similar structures of oval form. They may be either intra- or extra-cellular. Occasional forms will be met in which the pale structure of the body is projected in the form of a pseudopod; in which case the granules may

remain in the larger portion of the structure, or one or two may be found in the projection. These forms closely resemble the bodies shown in Fig. 2 of the article by Sjöbring in the *Centralblatt für Bacteriologie, Vol. 27.*

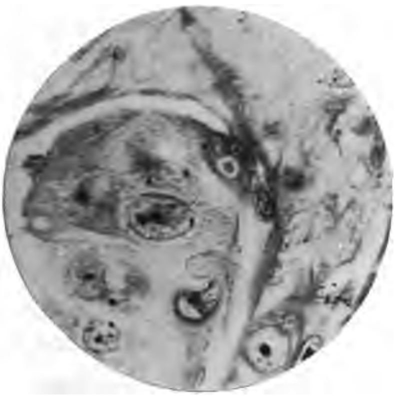
We have never been able to detect any change of form in the intra-cellular bodies, although scrapings from carcinoma in which they were found, have been exposed to various procedures. The extra-cellular bodies may be occasionally induced to change their form by placing the preparation in a thermostat. In this case we have repeatedly observed that bodies which were spherical changed on the warm stage after a period of some hours, and projected longer and shorter processes. Attempts to stain them in the fresh state have met with varying results. They apparently take on Sudon III, but Dr. Clowes, the chemist of the Laboratory states that this is not a genuine staining reaction.

We find that the organism of vaccine may be stained in the same manner, and we are informed that others have employed Sudan III as a stain for amoebae.

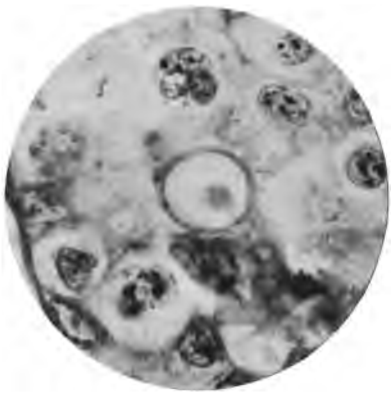
Attempts to fix the organisms by heat gave unsatisfactory results, owing to the distortion which they undergo. If coverslips be made and dried in the air, the small, spherical bodies will stain with any of the aniline dyes. The larger forms, however, remain unstained, and appear as spherical or oval clear spaces in the stained material of the coverslip. The best means to fix them is to make rapid smears after the manner employed in making blood slips and drop the wet cover-glasses into warm Hermann's fluid or sublimate. They may then be stained with Plimmer's method. We have likewise found that pouring peritoneal fluid which contained them into warm Hermann's fluid or sublimate, and treating the coagulum after



1.



2.



3.

4.

the manner in which tissue is manipulated, gives excellent results, the organisms retaining their form and characteristic appearance. (Plate XV, Fig 4.)

The best method for preserving the extra-cellular forms is by hardening masses of tissue which contain them. An excellent method for hardening the organisms with the pseudopodia projected, has recently been described by Eisen in his very excellent article in the Medical Record of July 7th, 1900. Dr. Eisen has been kind enough to forward us some of his sections, and we can heartily endorse what he has described in epithelioma.

In sections hardened in Hermann's fluid and stained with Plimmer's method, the bodies correspond very accurately to the description given by Plimmer. Some of the different types which we have observed are shown on Plate XV, Figs. 1, 2 and 3, and Plate XVI, Figs. 1, 2, 3 and 4. As to the staining qualities of the organisms, we find that they closely conform to those given by Plimmer—that is, that the central body and capsule of the structure take on a coppery red or pale rose color. In the case shown on Plate XV, Figs. 2 and 3, we have succeeded in staining the central bodies with the nuclear stain, and in some of the cell inclusions only the central portion of the central body takes the nuclear stain, and is then surrounded by a layer of protoplasm, which takes the rose or pink color.

The organisms may appear singly in the cells, or even in large numbers. (Plate XV, Fig. 3.) We have detected as many as 14 in one cell. These is no difficulty in detecting the structures in properly hardened and stained material. They can be readily distinguished from vacuoles in the protoplasm by the well defined capsule and central bodies, their relative uniformity in size, and occasional presence between the cells.

Summing up this phase of the question, it can be unhesitatingly stated that Plimmer's bodies present a characteristic appearance and can be readily differentiated from cell degenerations of the usual type and other structures which they might resemble.

To determine whether or not Plimmer's bodies could be due to cell degenerations, we have carefully examined a large number of sections of well-known pathological conditions of known cause, such as tuberculosis and certain bacterial infections, and a large number of animals inoculated with various pathogenic yeasts, and we can state that we have never detected any changes in the epithelial or other cells in this class of diseases which could be confused with Plimmer's bodies.

In attempting to determine the nature of Plimmer's bodies, the fact becomes immediately patent, in reviewing the literature, that many observers have depicted these structures. Scarcely an article has appeared in which the observer has not, more or less accurately, illustrated cell inclusions which are no doubt the characteristic bodies of Plimmer. The slight variations which are encountered in these illustrations are very likely due to the different methods of hardening and staining employed by the different investigators, and the usual subjective equation incident to all illustration by drawings. Figures which are unquestionably intended to illustrate bodies of this nature may be found in a publication of Sawtschenko, *Bibliotheca Medica, 1895, Abtheilung D II, Heft 4*. Those which most characteristically represent Plimmer's bodies are Figs. 18, 19, 30, 51, 57 and 60. In an article published by Jackson Clark, *Centralblatt für Bacteriologie, Vol. 16*, Fig. 6 of Plate III, is a most typical representation of these bodies. And in like manner, an investigation will reveal more or less characteristic illustrations in the publications of the majority of investigators.

Of especial interest in this connection are the illustrations of Sjöbring accompanying his most recent publication, in the *Centralblatt f. Bacteriologie, Vol. 27.* Fig. 1 of his article represents a section through the wall of a *vasa efferentia* in the epididymis. In the protoplasm of the epithelium are shown three typical Plimmer bodies. This illustration is especially interesting, as the author states it is taken from the epididymis of an animal from the neighborhood of a fragment of sterile carcinoma which had been implanted in the testicle.

It will, therefore, be seen that many of the observers who have described cell inclusions, in the belief that they were protozoa have unquestionably seen typical Plimmer's bodies, and it would appear as if Sjöbring, in his most recent publication, was dealing with bodies of at least a very similar appearance. In all the carcinomata which we have investigated, we have found that Russell's bodies could be detected, especially about the periphery of the tumor and in the enlarged regional lymph nodes, even when these were not carcinomatous. In sections stained with Plimmer's method, they take on a dense blue black, but by modifying the stain they can be made a brilliant red, which gives them much the same appearance as they possess when stained with fuchsin. In one case we have succeeded in staining the central bodies of the Plimmer inclusions, and are able to trace a direct morphological relation between Russell's bodies and Plimmer's bodies. In one case of adenocarcinoma of the ovary, which contained a large number of Russell's bodies and protozoan forms, the bodies which correspond to Plimmer's bodies were more or less atypical, probably owing to the hardening agent (sublimate).

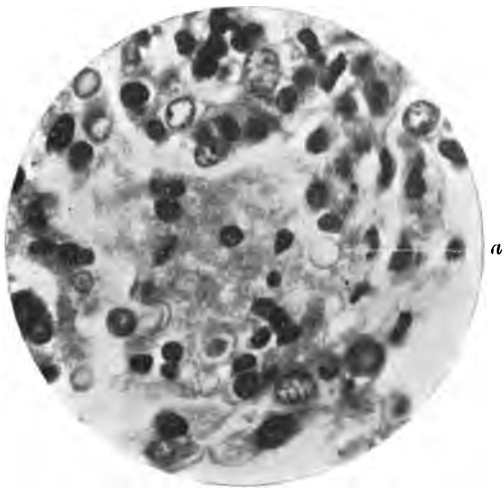
From the above, it will be seen that Plimmer's bodies are not new structures, but that his hardening and staining methods give them

a more characteristic appearance and probably differentiate them in a large number of cases in which, when treated by the ordinary staining methods, they would be invisible.

In form the bodies are almost always round or oval. Occasionally they occur in pairs, in which case they are usually smaller than the single bodies, and present an appearance which is highly suggestive of some form of division. Plimmer describes a budding form of the organism, which, in our experience, is very rare. We have only found one or two bodies which conform to this description.

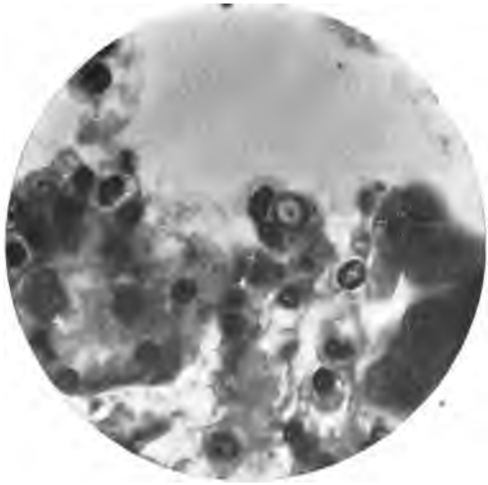
The fact that certain observers have succeeded in obtaining pure cultures of blastomyces from carcinoma, and the significant experiments of Sanfelice, naturally raise the question as to whether these organisms can be detected in carcinomata. In the examination of our cases, we have thus far failed to find any structures which we were willing to consider blastomyces. During the last two years, we have carried out an elaborate investigation of pathogenic yeasts, including Plimmer's organism, Sanfelice's neoformans and lithogenes, the pathogenic blastomycis isolated from a skin leision by Hektoen, and a similar organism isolated by Gilchrist and Stokes.

A summary of the results of a long series of comparative inoculations with these organisms, as well as a careful morphological comparison, will form the subject of a future publication from this Laboratory. The details of the results will not be entered into here. Suffice it to say that we have never detected a sufficient transformation in the organisms injected to give them an appearance identical with the Plimmer bodies of carcinoma. The nearest approach to such a result is shown in Plate XVII, Figs 1 and 2, which represent yeast cells (Plimmer's) in the lung of a guinea-pig, hardened and stained by his method.



1.

Plimmer's yeast in lung of guinea pig. Hardened and stained according to Plimmer's method. At *a*, an organism with single contour. (Oil immersion.)



2.

Field from same section as Fig. 1. Yeast with thick capsule in act of budding. Central bodies. (Oil immersion.)

Thus far, the distinguishing feature which we have always observed, has been the double contoured capsule of the yeast organism, which Plimmer's bodies do not possess. At the same time, we have occasionally noted yeast organisms with a single-contoured capsule; but in these cases they never presented an appearance which could be confused with a typical Plimmer body. Plate XVII, Fig. 1, shows a yeast organism with a single contoured capsule, which, it will be noted, contains no central body. *From a morphological standpoint, we have been unable to demonstrate the identity between Plimmer's bodies and transformed yeast organisms.*

The culture experiments in this Laboratory have been of a uniformly negative nature. An elaborate bacteriological investigation was carried out, by Dr. Pease, former bacteriologist to the Laboratory, at the time the tumors were being investigated for the presence of Plimmer's bodies, and in only one case did he succeed in obtaining a culture of a blastomyces. In order, if possible, to find a suitable medium for the blastomyces, in case the negative results were due to unsuitable substrata, he prepared and employed sixty-four different varieties, which it may be of interest to enumerate. In this list, the term + is used to indicate acidity, and — alkalinity. The figures indicate the units of acidity and alkalinity recommended by the Bacteriological Committee.

Bouillon neutral
Bouillon + 15.
Bouillon + 5.
Bouillon — 15.
Bouillon (sugar free).
Bouillon glucose.
Bouillon lactose.
Bouillon saccharine.
Bouillon glucose-tartaric acid.

Bouillon pig liver.
Bouillon pig-liver cancer.
Bouillon pig kidney.
Bouillon glucose-cancer.
Bouillon glucose-tartaric acid-cancer.
Bouillon dog-cancer.
Bouillon asparagin.
Bouillon potash soap.
Bouillon human glucose-neutral.
Bouillon tartaric acid-glucose (human).
Bouillon fucus crispus.
Agar neutral.
Agar + 15.
Agar — 15.
Agar potato.
Agar glucose.
Agar glucose-tartaric acid-cancer.
Agar beerwort.
Agar serum.
Agar hay.
Agar glucose-hay.
Agar glycerine.
Agar fucus crispus.
Agar cabbage water.
Gelatine neutral.
Gelatine 15.
Gelatine potash soap.
Gelatine beerwort.
Milk.
Serum bovine.
Serum human.
Serum dog.
Serum ascitic.
Serum hydrocele.
Serum abd. fluid.
Urine.

String beans in aqua dest.
String beans in Niagara water.
Bean stems-glucose-tartaric acid.
Beerwort.
Potato infusion.
Potato.
Hay infusion.
Hay glucose water.
Sugar water.
Glucose water.
Fucus crispus water.
Fucus crispus hay infusion.
Cabbage water.
Lettuce water.
Bread.
Human fat.
Casagrandi's medium.
Nahrstoff (Hayden).
Nahrstoff (Hayden) soda.

In our experimental inoculations of animals, we have usually been able to obtain the blastomyces by cultivation after the inoculation. The majority of lesions which we have produced have been those of a typical blastomycetic mycosis with abscess-formation, or characteristic granulomata containing the organism.

Having thus determined to our satisfaction that the yeast organism was not the essential cause of carcinoma and sarcoma, and could not be confused with the organism we had already observed in fresh scrapings of carcinoma and in our experimental animals, and having already convinced ourselves of the identity of the organisms found in the fresh state and the forms known as Russell's bodies, Plimmer's bodies and protozoan forms in the tissues, our attention was called to the possible relation between these inclusions in can-

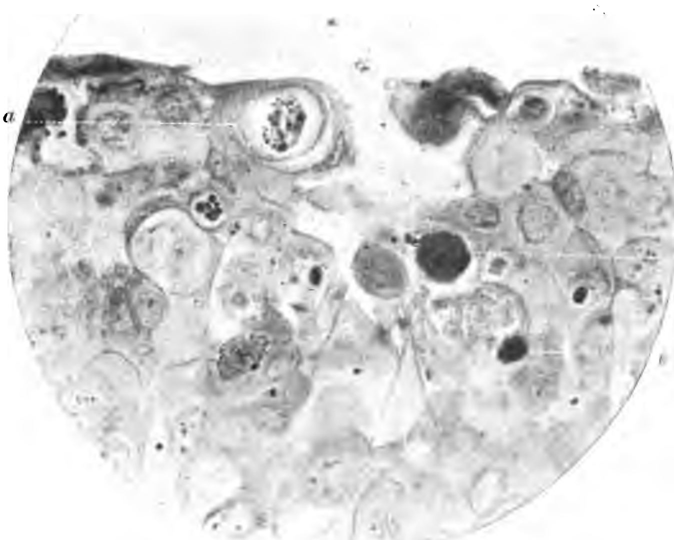
cer and the vaccine bodies observed after inoculation of the cornea with vaccine virus, by an article by Dr. C. Gorini, in the Centralblatt für Bacteriologie, Vol. XXVIII, No. 8/9, Sept., 1900, entitled, "Ueber die bei der mit Vaccine ausgeführten Hornhautimpfung vorkommenden Zelleinschlüsse und über deren Beziehungen zu Zellinklusionen der bösartigen Geschwülste." We had already noted the similarity of Russell's bodies to the illustrations of inoculated corneas, and it remained for us to harden and stain the cornea of rabbits which had been inoculated with vaccine virus after Plimmer's method. The result of our comparative test in this case shows, not only that the half-grown form of the vaccine organism is very closely related in appearance to the bodies of Plimmer, but that the bodies of Russell in carcinoma and the protozoan forms in carcinoma, all have their prototypes in the various stages of development of the vaccine organism. (See Plate XVIII, Figs 1 and 2.)

This striking confirmation of Gorini's observation was more than doubly confirmed when, after the recent announcement of Dr. M. Funk, in the British Medical Journal of February 23d, this year, on the cultivation of the vaccine organism, we repeated his experiment and found that the organism of vaccinia, while undergoing development, shows essentially the same phases we had already noted in the organisms observed in fresh scrapings of cancer and in the peritoneal fluid and blood of cancer cases.

Having thus convinced ourselves that the organism with which we were dealing was a protozoon belonging in the same group with the vaccine organism, it remains to be seen what evidence can be produced to show that these protozoa, which are a constant occurrence in the fresh material of cancer, and which we had cultivated and identified in the tissue under the form of Russell's bodies, Plimmer's bodies, etc., are the cause of cancer.

1.

Recent vaccination of cornea (third day). At *a*, young vaccine organism (analogous to Russell body) entering epithelial cell of cornea. Oil immersion.) (Plimmer's method.)



2.

Section of vaccinated cornea (seventh day). (Plimmer's method.) At *a* and *b*, bodies analogous to Plimmer's bodies ; *c* and *e*, younger forms of parasite. At *d*, a small organism within the nucleus of an epithelial cell.

The period which is alloted to us before the presentation of this Report will prevent our preparing a critical analysis of the large number of animals which we have inoculated with cancerous material and cultures of the organism from cancer. We have found it necessary to carefully restain the tissues of all our earlier animals with Plimmer's method, and, as this work is not yet complete, we deem it advisable to withhold the complete series until we are in a position to consider certain phases of the question which will require an investigation of tissues from other diseases, which are possibly protozoan infections.

That the protozoon of cancer is capable of producing, even in man, lesions of a very different nature from infection of the epithelium, seems to be strongly indicated by the following observation:

Case 108, Mrs. E., age 45. Well-developed cancer of right breast, with axillary lymph nodes, operated February 5, 1901, at Buffalo General Hospital, by Dr. Park. The case in question attracted our attention because of a pigmented pustule beneath the skin of the right axilla. The clinical notes, in brief, are as follows:

Three years ago observed a retraction of the nipple. Six weeks ago noted a well-defined tumor in the right breast. At the same time, a small nodule was felt beneath the surface of the skin of the right axilla. This developed in a region which was subject to irritation by the edge of the patient's corset.

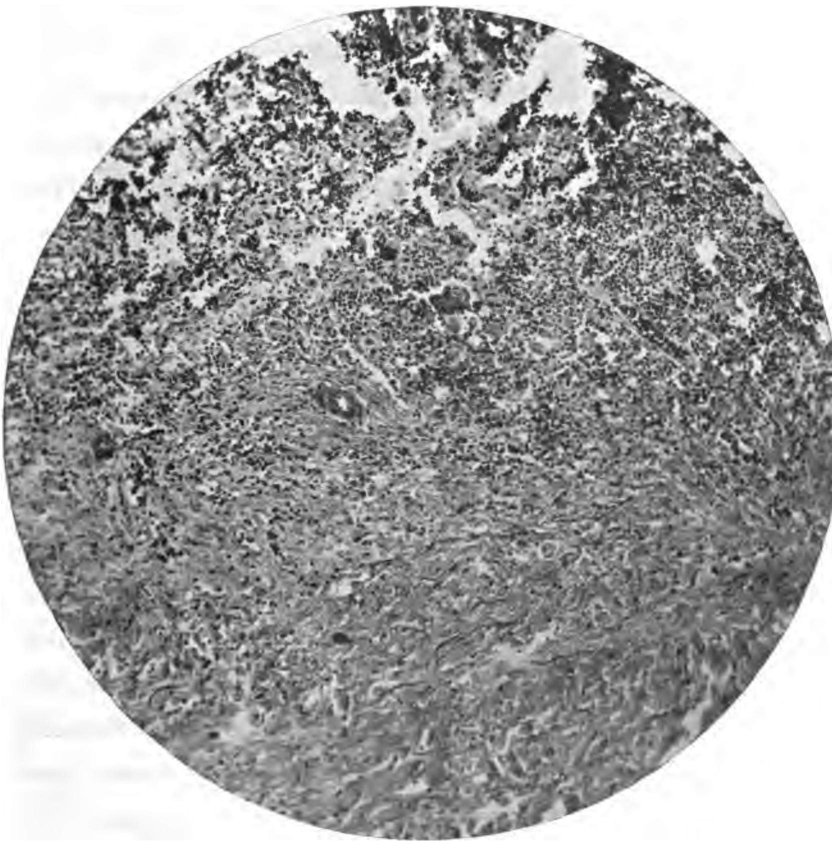
In removing the tumor, Dr. Park carried a flap up into the axilla, removing the axillary lymph nodes, and including the pustule above mentioned. The tumor reached the Laboratory one hour and a half after the operation. An inspection of the tissues removed shows them to consist of an enlarged right breast with a thickened and retracted nipple. The flap of skin removed is included between two curved incisions. At a distance of about five inches from the nipple,

there is an elevation of the skin somewhat larger than a pea. The skin covering it is glazed, and on palpation it is found to contain fluid. On opening this pustule, a small amount of dirty red fluid escapes. Examined in the fresh state with the microscope, this material is found to consist of leucocytes, red blood corpuscles, and a large number of cells, from five to ten times the diameter of a red globule, possessing coarse and fine granulation. Some of them contain highly refractive bodies somewhat finer than ordinary cocci, but the greater number have embedded in their protoplasm, poorly defined, hyaline, pale green, spherical bodies, somewhat smaller than red blood corpuscles. When treated with acetic acid, these hyaline bodies and the granules of the cells become more distinct, and nuclei may be made out. Besides these cells are a large number of ordinary pus cells, which form the principle constituent of the fluid.

On cutting into the breast, it is found to consist, for the most part, of fat, through which run sharply defined bands of carcinomatous tissue. At no point in the structure is a well-defined tumor mass. From the most vascular portion of the carcinoma fresh scrapings were made. Under the microscope these scrapings are found to consist of closely packed epithelial cells with vesicular nuclei. A large amount of free fat is found in the preparation, but the cells show very slight evidence of fatty degeneration. Between the fat droplets are a considerable number of small, greenish, hyaline bodies, which, in our experience, can be recognized from fat by the slight difference in refractive index and color.

Portions of the tumor were hardened in Hermann's fluid. On examining the axillary fat, a group of five or six enlarged lymph nodes may be detected. On dissecting these out and incising them, they are found to contain more or less extensive deposits of cancer. Sections of these were hardened in sublimate and Hermann's fluid.

PLATE XIX.



Embolic skin pustule from carcinoma of breast. Deeply stained spherical bodies are protozoa. (Low Power.)

Fresh examination of scrapings from these lymph nodes reveals the presence of bodies which correspond to what we have recognized as the fresh Plimmer body. They are composed of pale fluid protoplasm, and contain a group of fine granules. Their outlines are well-defined, and in many cases they appear to be sending out projections. In some of these bodies, the protoplasmatic granules show active Brownonian movement. An examination of the sections from the tumor and lymph nodes shows the case to be one of soft carcinoma of the breast with metastases in the axillary lymph nodes. Stained with Plimmer's method, a considerable number of the various forms already mentioned can be found—Russell's bodies, Plimmer's bodies and protozoan forms. A section through the pustule hardened and stained with Plimmer's method, reveals a most interesting condition. It consists of an abscess in the sub-cutis. Upon the surface the papillae of the cutis are normal, but directly above the abcess three or four of the papillae are seen to be hypertrophied and extend into the sub-cutaneous tissue. The abscess appears to be made up, for the greater part, of masses of spherical bodies somewhat smaller than leucocytes. There is no apparent inflammatory reaction about the periphery. The blood vessels show no engorgement. (See Plate XIX.) Under high dry power, the abscess is found to be composed of leucocytes with horse-shoe nuclei and a large number of spherical and oval, deeply stained bodies which closely resemble large Russell's bodies. (See Plate XX.) Besides the leucocytes and these small sperical bodies, are a large number of large oval and spherical cells with one or two nuclei. Many of these contain deeply stained spherical bodies, somewhat smaller than the free spherical bodies in the tissue. Others of nearly the same size contain a large number of small hyaline bodies

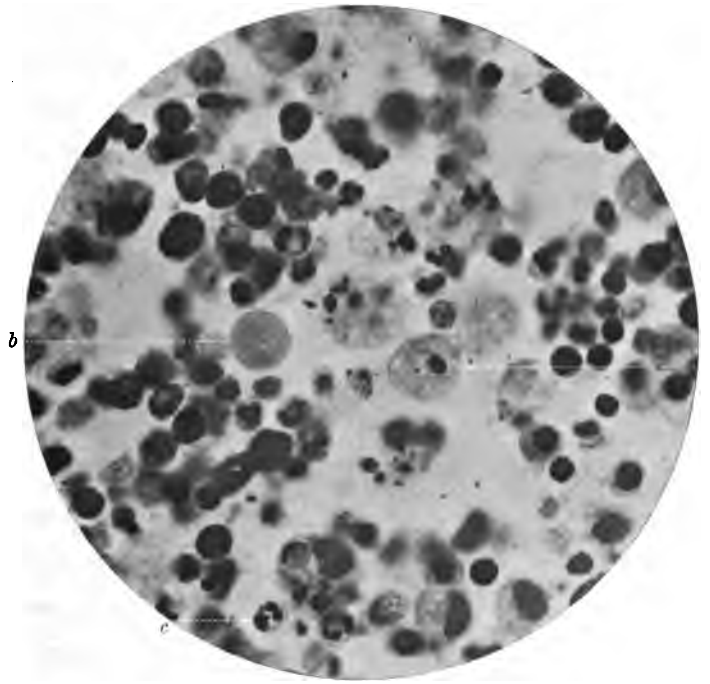
which do not take the stain. These, we are inclined to believe, are the sacs of the parasite. (See Plate XX.)

Besides the small forms and large sacs, we have found a number of spherical bodies, about four times the diameter of a leucocyte, which stain brilliantly with the Bordeaux red of the preparation. In a number of these bodies, we have found evidences which are strongly suggestive of segmentation, after the manner recognized in malarial parasites. The blood vessels within the focus contain, besides red blood cells, large numbers of the deeply-stained oval and spherical Russell's bodies. In some cases the endothelium of the capillaries is greatly swollen and contains one or more of these deeply stained bodies.

We are inclined to believe from this observation that this pustule is the result of embolic deposit of the parasites from the cancer of the breast, and we would interpret it, pending further observation, especially in the light of our animal experiments, as indicating that the organism of cancer is capable of producing other lesions than that of epithelial infection.

The material with which our animals were inoculated consisted of peritoneal fluid from cases of abdominal carcinosis, fluid from the interior of malignant ovarian cysts, sterile cancer, and dried sterile cancer and lymph nodes rubbed up with salt solution. Some of these latter contained metastatic deposits of cancer, but a number were simply the enlarged lympth nodes, in which we had already detected Russell's bodies. In each case the fresh material was carefully examined before, and the presence of parasites was determined. The presence of parasites was likewise verified in hardened sections of the material where this was possible. The following is summarized from the complete list of animals, which will appear in the second part of this communication.

PLATE XX.



Field from center of skin pustule, shown on Plate XIX. At the center remains of spore cysts. One at *a* contains a single deeply stained body (young parasite). At *b*, a half-grown organism stained red. *c*, a leucocyte. Remainder of field filled with young spherical and oval organisms and polymorph nuclear leucocytes. (Plimmer's method.) (Oil immersion.)

ANIMALS INOCULATED WITH MATERIAL AND CULTURES FROM CARCINOMA AND SARCOMA IN MAN.

2 guinea-pigs inoculated in the jugular with peritoneal fluid died in 22 and 19 days respectively.

14 guinea-pigs inoculated in the peritoneum with peritoneal fluid died in an average of 58 days.

1 guinea-pig inoculated in the right eye with peritoneal fluid died in 10 days.

1 guinea-pig inoculated in the jugular with filtered serum died in 304 days.

1 guinea-pig inoculated in the jugular with cancer mush died in 15 days.

4 guinea-pigs inoculated in the peritoneum with cancer mush died in an average of 57 days.

11 guinea-pigs inoculated in the peritoneum with dried lymph nodes died in an average of 45 4-11 days.

7 guinea-pigs inoculated in the peritoneum with sarcoma died in an average of 92 2-7 days.

2 rabbits inoculated in the ear vein with peritoneal fluid died in 93 and 17 days respectively.

1 rabbit inoculated in the ear vein with filtered serum died in 164 days.

1 rabbit inoculated in the peritoneum with cancer mush died in 292 days.

1 rabbit inoculated in the peritoneum with sarcoma died in 278 days.

1 rabbit inoculated in the mediastinum with sarcoma died in 41 days.

1 dog inoculated in the peritoneum with peritoneal fluid died in 64 days.

1 dog inoculated in the peritoneum with sarcoma died in 160 days.

ANIMALS INOCULATED FROM ANIMALS INFECTED WITH PARASITES FROM CARCINOMA AND SARCOMA IN MAN.

Pig 23, inoculated in abdominal wall with lymph gland and peritoneal fluid from Pig 16, died in 9 days. Case I, adenocarcinoma omentum.

Pig 55, inoculated in abdominal wall with several nodes from Pig 52, also portion of old original tumor, died in 4 days. Case LVII, squamous epithelioma of skin.

Pig 72, inoculated in abdominal wall with B-Pig 67-a, 2 cc. node emulsion in water, died in 37 days. Case L, enlarged axillary lymph nodes recurring sarcoma breast.

Pig 75, inoculated in abdominal wall with 2½ syringes B-Pig 66-a, nodes powdered in sterile water, died in 59 days. Case L, enlarged axillary lymph nodes recurring sarcoma breast.

Pig 73, inoculated in abdominal wall with 2 cc. nodes in water B-Pig 64-a, died in 48 days. Case L, enlarged axillary lymph nodes, recurring sarcoma breast.

Pig 76, inoculated in the abdominal wall with A-Pig 68-a, nodes powdered in water, died in 17 days. Case LXI, carcinomatous lymph nodes from axilla accompanying well-developed carcinoma of breast.

Pig 15, inoculated in the abdominal wall with 2 cc. fluid from peritoneum Pig 13, died in 8 days. Case XXIII, recurrent sarcoma thigh.

The points of interest are that 14 guinea-pigs, inoculated in the peritoneum with peritoneal fluid containing the organism, gave an average length of life of 58 days; four, inoculated in the peritoneum with cancer mush, gave an average length of life of 57 days; 11, inoculated in the peritoneum with dried cancerous lymph nodes, gave an average length of life of 45 4-11 days. Six guinea-pigs, inoculated with peritoneal fluid and lymph nodes from animals which were infected in the above manner, gave an average length of life of 29 days, a little more than half the length of time for the animals inoculated directly from man.

This unquestionably shows the increased virulence of the organisms after passing through one animal. We are continuing these experiments in modified form, and shall report upon them later.

The average length of life for rabbits inoculated in various regions with the different forms of material used, shows the greater resistance of this animal to infection. In our most recent experiment we have succeeded, by growing the organism in a collodion sac (suggested by Dr. Clowes), in the peritoneal cavity of a rabbit,

in so increasing the virulence of the organism that a healthy rabbit inoculated in the ear vein died of general haematogenous infection from the organism after a period of 15 days. (Rabbit 56 of the list.)

It will be shown from these experiments that animals are readily infected when inoculated with carcinomatous material as well as pure cultures of the organism. The peritoneal fluid used in all of these inoculations was bacteriologically sterile, and consisted essentially of a pure culture of the organism. Two animals, one guinea-pig and one rabbit, which were inoculated with filtered serum from which the organism had been removed, gave a respective length of life of 304 days and 164 days. The organs of these animals were free from parasites.

The macroscopic pathological findings in these cases were generally uniform. All the animals were greatly emaciated, and presented on opening the abdominal cavity, collapsed intestines, reddened peritoneum, enlarged peritoneal lymph nodes, and a moderate amount of clear, straw-colored fluid. The lungs were dark red in color; collapsed heart contained but small amount of blood; the spleen was enlarged and reddened. The liver in many cases was hyperaemic, and the kidneys were generally injected. One dog, Dog 18, presented a large lymphoma of the spleen. This case will be considered separately. Dog 8, inoculated from sarcoma, Case 23, shows typical metastases of sarcoma in all of the regional lymph nodes.

In almost all cases a fresh examination was made of the peritoneal fluid, the organs, and the blood, and wherever made large numbers of the parasites could be readily detected, as already described.

Two guinea-pigs and two rabbits inoculated in the jugular with peritoneal fluid; show macroscopic lesions in the lungs very closely resembling those reported in our Fig. 1, that is minute white dots scattered through the pulmonary structure, usually localized in the neighborhood

of the bronchi. Sections from these lungs, stained with haematoxylin, show the presence of multiple beginning adeno-carcinoma of the bronchi.

These we should interpret as beginning adeno-carcinoma of the lung in four animals, making, with our Case 1, five animals in which the injection has been followed by infection of the bronchial epithelium. One guinea-pig, besides the five animals already enumerated, presents a condition of the lungs and liver, which we wish to interpret as primary carcinoma of those organs, and one dog presents a lymphoma of the spleen, the size of a large hazelnut, which we also attribute to the inoculation of the animal with dried lymph nodes from a case of carcinoma.

We have, thus far, restained with Plimmer's method, 40 of our 72 animals, and we find in all of the organs thus far examined, large numbers of the younger and more mature forms of the parasite. The lungs of all of these animals show that the parasites have penetrated into the epithelium of the bronchi, causing atypical proliferation in many cases, with breaking-through of the basement membrane, and penetration into the deeper structure of nests of epithelium. In case of Dog 18, lymphoma of the spleen, this tumor is found to contain areas composed of pure cultures of the organisms. In the case of one guinea-pig, Pig 22, with primary carcinosis of the liver, the epithelial cells of the liver are found to contain the young forms of the parasite.

When we have completed the restaining of the organs of these animals, according to Plimmer's method, a complete and careful report will be made as to the more complicated histological findings.

In the succeeding portion of this paper consideration and recognition will be given the work of L. Pfeiffer, Juergens, Sjöbring, Schueller and Eisen.

The Importance of Chemical Research in Investigations Regarding the Cause and Methods of Treatment of Cancer.

By G. H. A. Clowes, Ph. D.
Biological Chemist.

In a work of this description, verging, as it does, upon the border-line of several sciences, it is by no means an easy task to outline clearly the scope and application of pure chemistry. We should rather prefer to commence by showing how important a role chemistry, in conjunction with other sciences, has played and is playing to-day in the elucidation of numerous medical problems; and then proceed to a careful consideration of the means whereby the methods and theories of this science may be applied with advantage to research in the field of cancer.

In all physiological, biological and pathological processes, we have to deal with complex chemical changes; changes which, so far as their intramolecular action is concerned, are not at present clearly understood. Problems are introduced which may no longer be relegated exclusively to the domain of an exact science, such as chemistry or physics, but in which the biological factor of the living cell plays an all-important role. In many respects we may look upon chemistry as the groundwork upon which many other sciences are established; and the application of precise physico-chemical methods and reasoning has, in many notable cases, led to the elucidation of questions previously unsolved by medical men

or biologists. It is, therefore, in the application of chemistry to medicine in all its branches, rather than to pure chemical research, that we must first look for results. There can be no doubt that, although we may not at first sight be able to interpret the true significance of each new laboratory discovery in the field of physiological chemistry, yet we may rest assured that each one of these results, viewed in the light of future generations of scientists, will contribute toward the elucidation of what appear to us at the present day to be unfathomable problems.

At this point a brief reference to the historical aspect of the case may not be amiss. As examples of exclusively scientific men who have introduced their ideas and methods into medicine with great success, we may mention Liebig, Pasteur, Ehrlich, Fisher and Ducleaux. It is interesting to note how Pasteur, unfettered by any preconceived notions of pathology, faced and solved the greatest problem of his day, building up the branch of medicine known as bacteriology, and introducing a clear conception of parasitic organisms as the cause of disease; of the toxins (or poisons) which they produce; and of the anti-toxins (or counter-poisons) which may be elaborated by the system itself in order to counteract the inroads of the former. To his early training in research of physics and chemistry, together with his original experimental methods, may be attributed the vast success of Pasteur, in a, to him, entirely new field. Passing to men of a different type, in Fisher we find a great chemist who, after a few years' successful work in connection with the aniline dyes, etc., turned his attention to the then extremely important problems associated with the constitution of the sugars. After exhaustive and conclusive work leading to the complete classification of the carbo-hydrates (sugars), together with a clear conception of their stereo-chemical relationship, Fisher

devoted his attention to the proteids (another most important factor in the human economy); and his work on the purin bases and enzymes bids fair to place medicine upon an infinitely better footing regarding the nature of the processes which evolve themselves within the system, than was possible before we were in any sense acquainted with the chemical constitution of these bodies. In this connection an epoch-making work was that of Kühne and Chittenden, on the proteids and their decomposition products, but as it will be impossible to refer in detail to the numerous investigators in this field, we must pass on to other considerations.

Ehrlich has recently enunciated a theory regarding the nature of the toxins and anti-toxins which, based upon purely physico-chemical considerations, met with much scepticism, but has proved itself a good working theory and one likely to lead to fruitful results. Ehrlich it was who first conceived the idea of removing the uncertain physiological factor involved in experimentation with animals by testing the efficacy or otherwise of toxins by their action on blood corpuscles suspended in aqueous salt solution in a test tube.

It is probably to a certain extent due to the rapid strides made by chemistry, outdistancing, as she has, her sister sciences, that we may attribute the attention being paid by chemists to problems belonging more or less to other fields. In so doing, the first work of the chemist is to bring himself into touch with physiological and other investigators, a by no means easy task. Even a common ground is difficult to find. A chemist accustomed to mathematical precision of thought and experiment is at first liable to lose himself in the uncertainty of all problems in which the factor of life plays so great a role. But success frequently attends him, and we now find numerous physiological phenomena to be due to definite

chemical reactions. Of late years, physical chemistry has also played an especially important role in these respects; the laws of osmosis, chemical mass action, of thermo-dynamics and the modern electrolytic theory of solutions, having opened up previously untouched fields of research. In fact, it is hardly too much to say that medical research of the future will run, to a large extent, on the lines of chemistry, especially from a theoretical standpoint. At the same time, chemical methods are fast being adopted by those engaged in scientific research in this subject.

In pathology the chemist is called upon to explain most of the reactions due to enzymatic and other chemical changes, and he has also been of great assistance in helping the pathologist to obtain a true conception of the significance of many of the microchemic reactions obtained on fixing, staining and otherwise experimenting with pathological specimens. The pathologist is only too apt, working with preconceived ideas and rooted convictions, to fall a victim to serious errors when dealing with the complicated problems involved in connection with microscopic examination of specimens. He is too apt to subordinate observation to experiment. Knowing but little of the chemical nature of the hardening materials and stains which he employs, he is very apt to place too much significance upon questions of form and color. Only recently a book has been published by an eminent German botanist, dealing with this question of artifacts, and showing how readily the most conscientious observer may be misled by trifling accidents.

But it is, perhaps, in the fields of bacteriology, hygiene and antisepsis, that chemists have recently rendered the most valuable services to medicine. These sciences have practically been created as an adjunct to chemistry. As mentioned above, the proper conception of bacteria as parasites, of toxins and anti-toxic treatment,

is all to be attributed in the first place to the physico-chemical investigations of Pasteur and his school. Bacteriology can only be carried on successfully by determining the chemical nature of the media which are favorable or otherwise to the growth of various organisms. For this purpose, minute chemical analyses of the tissue or other media in which the bacteria live, and also of these organisms themselves, are necessary. Further, in the investigation of the nature and properties of toxins or enzymes, and the separation of these bodies and of the products due to their action upon starches, fats, proteids, etc., the chemist alone is in a position to undertake the work.

How bacteria, together with such bodies as toxins, alkaloids and ptomaines, associated with them under pathological conditions, may be destroyed without injury to the subject, is another problem which we are called upon to face. Regarding the nature of anti-toxins and the conditions most favorable for their production, the work of Ehrlich previously referred to, has afforded most valuable information. It is not absolutely beyond the bounds of reason that chemistry may, in the future, arrive at a synthetical production of many of these bodies, as has been so widely the case in the less complicated fields of organic chemistry. Further, in those cases in which destruction of bacteria and their toxins appears to be impossible, we have to consider the possibilities of at least limiting the process of their development by means of simple chemical agents under varying conditions. Here arises once more the disturbing physiological factor, in that we can never be sure that two individuals, apparently identical, will react in the same manner towards a given quantity of chemical material, as would be the case in exact chemical reactions. We know toxins to be the direct excretory products elaborated by bacteria, just as the enzymes, or unorganized

ferments, (invertase, for example), are elaborated by yeast. In fact, toxins may be looked upon as enzymes, and the nature of all classes of enzymes is being very closely investigated at the present time. One of the most effective means at our disposal is the Buchner's press recently introduced into this work in its most perfect form, by the discoverer of the enzyme producing alcoholic fermentation in yeasts. On grinding up the bacteria with quartz sand and diatomaceous earth, one is enabled to rupture their capsules and membranes, and, by means of a hydraulic press, to obtain a fluid extract containing these enzymes. The chemist is not merely content with proof of the presence of toxin or toxic bodies. He devotes his attention to the problem of subdividing these bodies and determining the chemical nature and physiological properties of each one of the numerous constituents usually met with in any such mixture.

Of the chemical processes that take place in the living organism, we have at present but a very limited knowledge. The study from a chemical standpoint of the reactions that take place in the stomach and intestinal tracts, is one of the most vital importance. We have but a hazy conception of the nature of those enzymes or ferments, which, as in the case of pepsin in the stomach, or of trypsin in the pancreas, play the role of digestive agents, breaking down complex molecular masses into simpler, more readily diffusible bodies, which, once more, on entering the system tend to reunite and form complex syntheses. Chemistry now looks upon all this type of enzymotic processes as those of simple hydration and dehydration—as, for example, the splitting up of starches to form sugars, and of proteids to form albumoses and peptones, and vice versa. That enzymes may be looked upon as definite chemical bodies is, for the oxydases (the oxidation-producing group), pretty conclusively

demonstrated. It is merely due to the extremely unstable nature of their molecular equilibrium that they so readily undergo decomposition, and their ability to function as catalytic agents is probably due to the same cause. By "catalytic agent" is meant one which is capable of bringing about the decomposition of other bodies without itself undergoing any appreciable change, so far as its final state is concerned. Bacteria are known to produce enzymes of a similar nature to those enumerated above, and their toxic action in cases of marked cachexia may be attributed as much to the abnormal breaking-down of body material as to any other cause, the bodies thus produced acting in a manner prejudicial to the system. For it is well known that even the simple products of peptic digestion are, when introduced into the blood current, extremely toxic, causing fever, fall of blood pressure, or death.

Another extremely interesting, but far more difficult, field of investigation is that of the chemical processes taking place in connection with the excretion of the ductless glands. Physiology has proved that the thyroid plays an important part in the nutrition of the body, and its extirpation has led in many cases to death. Chemical research has shown that the essential constituent of this body is an iodine-containing body of definite constitution and endowed with very marked physiological characteristics. Also the work of Professor Abel and other investigators, upon the chemical nature of the various constiuents of the suprarenals leading to the isolation of bodies possessed of a specific constitution, is, from a chemico-physiological standpoint, one of extreme interest.

Urine, being most readily obtainable, and offering better facilities for investigation, has been far more exhaustively treated than any other products of excretion. In carrying out investigations on the nature of the constituents of urine, the first problem to be con-

sidered is that of the form under which the nitrogen is removed from the body. We have to determine the proportions of urea, uric acid, ammonia, creatinine, the alloxuric and xanthic bases, the amido acids, if present. We have to determine the total quantity of nitrogen excreted, and if the nitrogen contained in the various bodies of known constitution is not found to be sufficient to account for the total nitrogen obtained, we must endeavor to discover to what cause this deficiency is due; to detect some previously unknown nitrogen-containing base or acid, and if this be the varying constiuent of the urine, to determine its chemical nature and phyiological action. Further, the examination for indican and other products of putrefactive action in the intestines must be carefully carried out, and quantitative figures obtained. Pigments from the bile, and others, such as melanin, must be examined. The presence of such bodies as acetone and diacetic acid, must not be disregarded. Of course, the normal constiuents of urine—sulphates, phosphates, chlorides, etc.—and the abnormal—such as sugars and albumin—would in any case be determined. The utility and cause of the Ehrlich diazo reactions must, in all cases, be thoroughly investigated, as well as that of all such color reactions, the nature of which is not clearly understood.

Thus, to summarize this portion of the subject, we see that by thus combining minute and detailed experimental work with a keenness to observe and a readiness to note everything, the role of the physical chemist in medicine is more or less that of an elaborator. He collects the material offered to him by medical men, pathologists and biologists, systematizes that which will be of use to him, discarding that which has no bearing upon the problem; for the scientific portion of his work cannot be commenced until the allied sciences stand upon a correct chemical basis. With sufficient ex-

perimental facts and data at his disposal, he may be expected, from a scientific standpoint, to form an impartial judgment on these facts, and develop such working theories and methods of investigation as may be useful in the advancement of our knowledge of the subject.

In order to clearly define the possible fields of investigation in which a chemist may hope to obtain results regarding the nature and mode of cure of cancer, the problem will most readily be treated under a series of different heads:

1-(a). In conjunction with bacteriology.—In the bacteriological department of the subject, it is necessary to eliminate all cause of uncertainty, by making attempts to obtain growths of organisms from all sorts of tumors upon a large variety of media, a special study being made of the chemical nature of the tissue in which the organisms presumably exist, if present. Knowing the nature of this material, we are in a better position to prepare culture media having as nearly as possible the same composition as that of the media in which the organism may be supposed to have previously existed. Also it is very important to vary the conditions of experiment as much as possible. We must avail ourselves of those conditions most favorable to the supposed organism, such as enclosing the material in a collodion capsule before introducing it into the peritoneal cavity of an animal, in order to protect the parasites, if present, against the action of phagocytes and other bodies designed to defend the tissue from the inroads of invaders, thus facilitating their development and acclimatization. It is important that all possible forms of organisms should be considered, and the media found by previous experiment to be most suitable for their growth employed, in order that, if they be present, results may be obtained. In addition, the possibilities of the existence of symbiosis must be

considered. By "symbiosis" is understood a combined growth of two parasites, or of a parasite in conjunction with the tissue cells, in such a manner that each of the organisms in question affords valuable assistance to the other in their mutual development.

(b). Further, in this same department we must use all possible endeavors to produce tumors through the action of well known outside agencies, such as various forms of fungi, yeasts, protozoa and bacteria. We must study their normal mode of existence, and provide them with those conditions most favorable to their reproduction and acclimatization in animals. If tumors are produced, they must be compared with those obtained normally in cancer, since, if they should prove identical, they afford us a ready means of studying possible methods of prevention; but this part of the subject having been dealt with more thoroughly in a previous portion of the report, will not be further considered at this stage.

2. The bodies found in tumors and examined minutely by pathologists must be studied from a *micro-chemical standpoint*. The correctness of the conclusions drawn by pathologists as a consequence of the results obtained by various hardening and staining methods, must be gauged from a chemical standpoint. If possible, investigation should be carried on on a larger scale regarding the chemical nature of the bodies under dispute. And, above all, it is of the utmost importance, as mentioned previously in this paper, that the errors due to artificial effects obtained by the processes employed, should be detected, and thus resulting errors of deduction avoided.

3. The isolation of toxines.—An attempt should be made to isolate bodies of this nature from the tumors, by expression, and in order to insure the complete disintegration of the cell walls of any organisms present, in order that toxines contained in their interior

may be set at liberty. For this purpose, use may be made of Buchner's press, the nature and application of which has been explained above.

4. In cases of marked cachexia in which the influence of some body or bodies excreted from the tumor is exerted at a distance from the tumor itself, *we must especially search for toxines* and other products of bacteriological or enzymatic disintegration of the tissue, not only at the site of the tumor, but throughout the system in the blood and urine of the patient. In this respect the influence exerted by these bodies present in tumor extracts and blood of cachectic patients, upon the blood pressure of normal animals into whose circulation they are introduced, may be made of great assistance both as a means of detection and identification.

5. Investigation not only of the toxicity, but also of the chemical nature of the blood and urine of cachetic patients, as compared with that of normal individuals must be made. The toxicity of the whole, and of various fractions of blood and urine separated by differential chemical reagents, must be determined. The method adopted is that of intravenous injection of the urine, or other solution in question, into a guinea-pig or rabbit of definite weight, the symptoms obtained and the amount of material required to cause the death of the animal within a definite time limit being carefully noted. Knowing the weight of the patient and the quantity of urine excreted in 24 hours, we are then in a position to state authoritatively that the 24-hours' excretion of a definite body weight is capable of destroying one kilogram of the animal in question. Such a method of procedure affords us a definite standard of toxicity. Having determined which fractions, if any, are more toxic than under normal conditions, we must carry out special chemical investigations to find out what is the chemical nature of the bodies to which this action is due.

6. Having made minute chemical analyses of blood and urine associated with physiological experiments, with determinations of their toxicity, we have not only to compare the relative proportion of substances in the pathological materials with those obtained under normal conditions, but to search for any bodies found only under these conditions. Having obtained such bodies, either in the nature of toxines, alkaloids, amido bases or acids, it must be our endeavor to elucidate their chemical constitution. We must determine the molecular weight and the constitution of the molecule as a whole, of which they are composed. We must seek out the individual radicals in those molecules to which toxic and other effects may be attributed.

7. We must seek to discover characteristic tests for these bodies whereby they may be readily detected and thus serve as a means of early diagnosis.

8. We must endeavor, if they be toxines, to produce anti-toxins, whereby their influence may be counteracted, by introducing them in ever increasing doses into animals, and then making use of the serum of those animals as a means of establishing immunity.

9. If the bodies are of a definite chemical nature, and having, so far as possible, determined to which chemical groups in the molecule their toxic activity is due, we must make use of those chemical reagents capable of counteracting the influence of these particular groups, thus defending the organism from their attacks.

10. In dealing with this question of the minute examination of excretory products, perhaps one of the most important and, at the same time, elaborate pieces of work, one requiring a large amount of time and patience, together with close supervision and accuracy of methods, is the solution of the problem of metabolism involved in a large number of individual cases. We must carry out an

elaborate series of analyses of food supplied to patients and excretory products obtained under varying conditions of experiment and during long periods of time, with a view to finding what bodies are retained, if any, and in what proportion, and what bodies are excreted in excess of those supplied. By this means we may hope to obtain an insight into the dietetic treatment which would be most suitable to counteract the progress of the disease. Further, we may be able to draw conclusions as to the relationship existing between various forms of cancer, and a procedure of this sort may be of value in leading to an early diagnosis. Such experiments have been carried out in simple form, but never under such conditions as to be absolutely conclusive, and unless the methods employed are absolutely accurate, no confidence can be placed in the results.

Thus, to summarize the work previously mapped out, it is our intention to carry on our work rather on the basis of modern physico-chemical theories, than that of stereotyped bacteriological ideas, which, in the hands of numerous in vestigators in this field, have given but little result. We shall attempt by any of the means above referred to to discover the cause, and then be in a position to at least diagnose at an early stage with greater facility, the presence of cancer, and, if possible, working on the same lines, to determine the means of combating it. But, at the same time, it is our intention to carry on parallel experiments, disregarding the cause, but by empirical methods attempting to effect a cure on lines similar to those adopted by Pasteur in some of his best known work.

Up to the present, being provided with only temporary quarters, and having been in existence but a few months, the chemical department of the State Laboratory has carried on its work under

considerable difficulties, and has been principally engaged in solving chemical problems connected with the bacteriological and other departments. Considerable work has been carried out regarding the nature and conditions of existence as parasites, of a series of well known yeasts, and the chemical nature of their excretory products. Tumors have been examined for parasites, toxins and products of chemical decomposition. Analyses of urine have also been carried out in considerable quantity, intended to show wherein the normal constituents of the urine deviate in the case of cancer from those in other pathological cases, and under normal conditions. Further, considerable efforts have been devoted, on lines to a certain extent original, to isolate and determine the nature of any toxic bodies present in the urine of cancer patients. Investigations have also been commenced regarding the chemical nature of certain transudates and pigments associated with various forms of the disease.

Further, chemical examination of metastatic deposits of cancer derived from organs or tissues having a specific chemical constitution, such as tumors derived from adrenal bodies, and a comparison of their chemical and physiological constitution with the latter, are being carried out. Owing to the unfavorable conditions under which the work of the Laboratory is conducted at present, in temporary quarters, it has been found impossible to deal in any sense effectively with some of the more delicate phases of the subject. However, considerable attention is being devoted to the work of summarizing the publications of previous investigators, and, so far as possible, confirming their results, in order that on the completion of the new quarters being provided for this department, where all possible arrangements are being made for suitable accommodation and apparatus, no time shall be lost in proceeding to the thorough investigation of the subject.

Cancer Distribution and Statistics in Buffalo for the Period 1880-1899, with Reference to the Parasitic Theory.

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With the real or apparent increase of cancer throughout the civilized world, at a rate which gives cause for alarm, renewed interest has been aroused in this dread affliction, and in many countries laboratories are being established for the scientific investigation of the nature and cause of cancer, and societies are being organized for the statistical study of the disease.

The question of paramount importance is whether cancer is or is not a parasitic disease, as upon the answer to this broad question depend the special lines of research that are indicated for elucidating the exact cause and the control of the disease.

It must be admitted that up to the present time no convincing scientific demonstration of the parasitic nature of cancer has been adduced and generally accepted, though certain most interesting and suggestive findings have encouraged the hope that the pathologist might be close on the trail of the real agent of the disease. Such scientific evidence taken in conjunction with much indirect and cumulative evidence derived from many sources, has given good reason for holding tentatively the theory that cancer is parasitic in origin, and for pursuing its study upon this theory. In the mean-

time and before definite assurance is had that cancer is the result of parasitic infection, no line of study should be neglected that offers any prospect of elucidating the main question of parasitic origin.

Next to the direct scientific study, the most promising field of research seems to lie in the statistical study of the disease, in the collection and analysis of observations on the distribution and spread of the disease and its relation to race, social and economic condition, and natural environment. The latter method of study has already yielded most important clews for the parasitic theory, and if carried out systematically and extensively might perhaps result in the establishment of this theory beyond reasonable doubt. The history of medicine offers many examples of the establishment by indirect methods of study, by cumulative evidence, observations, statistics, etc., of the parasitic or infectious nature of different diseases in advance of the scientific demonstration of such.

Guided, then, by such thoughts and by the work of others along this line, the writer was induced to undertake the investigation here recorded with a view to ascertaining whether the statisical sudy of cancer in the city of Buffalo offered any support for the parasitic theory of cancer, or furnished any incidental side-lights that were of interest to the subject. The main purpose was to find whether there occurred in the city any *local foci of the disease* in special regions of the city or in certain houses, out of proportion to the population of such places, and in case such foci occurred, what relation existed between them and their natural environments and the conditions of race, social status, and habits of the population. So far as the writer is aware, no similar investigation on so large a scale has been attempted, for a large city, though the same principle has been applied by a few investigators in small towns and villages in Germany, France and England. Of the various previous investigations, none

is so striking and important as evidence for the parasitic theory as that of Behla* at Luckau in Germany, which has attracted wide-spread interest and attention. It seems well, therefore, before stating the results of our investigation in Buffalo, and as indicating somewhat the lines that our study has followed, to give a brief summary of Behla's work as follows:

Behla's Observation.—The town of Luckau consists of a central main portion with 3,000 inhabitants, flanked on the east and the west respectively by subdivisions of the city or suburbs (vorstadt), called the Kalau and Sando suburbs, each with a population of 1,000, making a total population of 5,000 for the entire town. During a period of twenty-two and one-half years (1875–1898), no cases whatever of cancer were noted in the western suburb, Sando; cases were not infrequent (nicht selten) in the central main town, and 73 deaths from cancer (cancer of the stomach and liver predominating) out of a total of 663 deaths from all causes occurred in the eastern suburb, Kalau. Cancer, therefore, caused 1 out of every 9 deaths in the suburb, Kalau, as against 1 out of 25 to 30 in the entire town, whereas no cases at all occurred in the western suburb, Sando. In Prussia, as a whole, the mortality rate from cancer was 1 to 30–50. During the last year and a quarter of this period cancer claimed 10 victims in the suburb, Kalau, or 1 out of every 100 inhabitants.

During the period of twenty-two and one-half years the number of inhabitants and their habits of life remained the same. The population was agricultural and lived on the products of its own gardens and fields. The dwellings were similar in kind and size and were generally damp. The soil of the suburb, Kalau, and of the central town was

* Robert Behla. Ueber vermehrtes und endemisches Vorkommen des Krebses. Centralblatt f. Bak., Parasit., u. Infekt., 1898, B. XXIV, Abteil. 1, S. 780, 829, 875, 919; and Die geographisch-statistische Methode als Hülfsfactor der Krebsforschung. Zeitschrift f. Hygiene u. Infectionskrankheiten, 1899, B. XXXII, S. 123.

flat, low, and moist; that of the suburb, Sando, was elevated, sandy and dry. The special distinction of the three divisions of the town consisted in the location of a ditch (graben), which, deriving its water from a stream on the west below the suburb, Sando, without touching this suburb, closely encircled the central town and the eastern suburb, Kalau. Cancer followed the course of this ditch, occurring not infrequently in the central town chiefly among those whose gardens bordered on the ditch, and most frequently in the eastern suburb, Kalau, all the gardens of which were watered from this ditch. In the suburb, Sando, which was not touched by the ditch, no cases of cancer were known. The suburb, Kalau, which we may designate as the *cancer-suburb,* consisted of a main street with two cross streets, containing 127 houses, whose gardens in general backed upon the surrounding ditch. Of the 127 houses, 56 were cancer houses, 43 representing a single case, 10 two cases, 2 three cases, and 1 four cases.

Behla's opinion was that the peculiar and unequal distribution of cancer through the different parts of the town of Luckau could be explained only by reference to the location of the ditch. In the cancer-suburb the gardens were all watered from the ditch, which contained stagnant foul water, and the people were in the habit of rinsing the vegetables grown in their gardens in water taken from the ditch. Behla believed that the garden vegetables became thus infected and in turn infected the people with cancer. He considered the various conditions of life and habits among the people, and focused down to the uncooked garden vegetables, of which large quantities were eaten raw, as the most probable source of infection.

It is evident that such observations as the above, if correctly and carefully made, and if multiplied so that the factor of chance be eliminated, must be regarded as strong evidence, if not as proof, of

the parasitic origin of cancer. With this striking example in mind, as well as many other somewhat similar observations, showing the irregular distribution of cancer and its tendency to occur in foci, resembling the well-known endemic foci of other infectious diseases, the writer undertook to ascertain the distribution of cancer in the city of Buffalo during the twenty-year period, 1880–1899, inclusive, with the results shown in the accompanying map of the city and the following tables and facts.

The statistics were collected from the original official certificates of death, signed in each case by a physician, preserved as the mortality records of the board of health of the city of Buffalo. To select out of these records only the cases of malignant disease required the careful examination of all death certificates or (in some years) the transcribed individual records of the same. In performing this tedious examination of the records and collecting the material pertinent to this inquiry, the writer received the assistance of Dr. Lawrence Hendee, of Buffalo, to whom he takes pleasure in acknowledging his indebtedness. Such cases only were collected as were shown by the death certificates to have had as the primary or accessory cause of death malignant tumor, under any of its various appellations, e. g., cancer, carcinoma, epithelioma, sarcoma, malignant growth, etc. A separate card for collecting the statistics of each case was used, covering the following points of inquiry:

Name.

Age, years, months, days.

Sex.

Color and race. Single, married, widowed.

Cause of death.

Accessory cause of death.

Place of birth.

Father's name and birthplace.

Mother's name and birthplace.

Place of death.

Date of death.

Occupation.

How long resident here.

Last place of residence.

Physician reporting.

With respect to residence the cases may be classified as follows:

1. Those dying at home, whose residence in the city (street and number) was given.

2. Those dying in public or private hospitals, usually following operation, whose residence in the city (street and number) was given.

3. Those dying in public or private hospitals, whose residence was not stated, who were buried in Buffalo, and whose city residence was found in the records of the institution where death occurred or in the city directory.

4. Those dying in hospitals, without ascertainable city address, and buried in Buffalo.

5. Those dying in hospitals or lodging houses, without city address on death certificate, on the hospital records, or in the city directory (year of death and year preceding death); buried outside of Buffalo, as shown by the records of the city or of the institution where death occurred.

6. Those dying in Buffalo, whose residence was stated to be outside of Buffalo.

Of these six classes, numbers 5 and 6, regarded as non-resident and including 114 cases, are entirely excluded from further consid-

eration in the following statistics; numbers 1–4, including 2,299 cases, are regarded as resident and are used as the basis of the following statistics and tables; and numbers 1–3, including 2,005 cases, whose city residence is known, are plotted on the city map according to the residence of the cases. The number of deaths from malignant disease, by years, classified by certain facts of residence, is shown in Table I.

TABLE I.—*Showing the Number of Deaths from Malignant Disease Reported to the Buffalo Board of Health, Classified According to Residence, and by Year, for the Twenty Years, 1880–1899.*

	1880.	1881.	1882.	1883.	1884.	1885.	1886.	1887.	1888.	1889.	Ten years, 1880–1889.	1890.	1891.	1892.	1893.	1894.	1895.	1896.	1897.	1898.	1899.	Ten years, 1890–1899.	Twenty years, 1880–1899.
Classes 1-3—Resident cases, city address known (plotted on map)	42	47	56	58	68	94	61	87	100	97	710	112	108	97	103	133	121	140	155	170	156	1,295	2,005
Class 4—Resident cases, city address not known (not plotted on map)	8	9	13	9	9	6	9	6	9	10	88	17	18	15	14	16	24	33	21	21	27	206	294
Classes 1-4—Total cases accredited to Buffalo	50	56	69	67	77	100	70	93	109	107	798	129	126	112	117	149	145	173	176	191	183	1,501	2,299
Classes 5-6—Non-resident cases, not accredited to Buffalo and excluded from statistics below	....	....	....	....	....	1	3	3	5	1	13	2	1	7	3	14	11	18	10	16	19	101	114
Classes 1-6—Total cases from all sources reported to the Buffalo Board of Health	50	56	69	67	77	101	73	96	114	108	811	131	127	119	120	163	156	191	186	207	202	1,602	2,413

House Distribution as Shown on Map.—The distribution by residence through the city of the 2,005 deaths from malignant disease whose residence was known* is shown in the accompanying map of the city of Buffalo. Each colored dot represents a single case. Red and green dots represent respectively cases dying in the two decades, 1880–1889 (710 cases) and 1890–1899 (1,295 cases). Multiple cases occurring in the same house are indicated by red squares inclosing the dots representing such cases.

A glance at this map shows the irregularity of distribution of the dots—a sparseness in certain parts and a concentration in other parts of the city. A remarkable concentration is shown in those wards inhabited largely by foreigners and particularly by Germans. Is this concentration real, due to increased frequence of cancer in such parts, or only apparent, due to greater density of population in the wards showing the greatest number of dots? To ascertain this, the number of dots must be compared with the size of the population in each ward. As the relative distribution of population through the city has changed during the twenty years and the ward boundaries also were changed in 1891, there is no accurate method of estimating for the whole period the cancer rate based upon a common standard of population by wards, and only a rough approximation can be obtained. This has been done (Table II) by comparing the number of dots in each ward with the ward population of 1900 (U. S. Census) and thus obtaining the number of dots in each ward per 1,000 of population. The resulting ward rates, thus obtained, serve the purpose of indicating roughly the ward distribution of cancer based upon a common standard of population. The actual rates are less important than the general tendencies

* Correction for all changes in house numbers was made by references to the official records of such changes in the Department of Streets of the city of Buffalo.

shown by the rates, broadly considered. Those wards showing higher and lower rates than the average rate for all wards have been marked on the map, against the ward number, with a plus (+) and minus (—) sign respectively, indicating that the cancer rates in such wards were high or low.

TABLE II.—*Showing the distribution of cancer by wards and according to the relative population of wards.*

WARD.	Population (1900).	Cases.	Cases per 1,000 of population (1900).	Per cent. above or below average rate.*
1	6,488	36	5.5	—17 per cent.
2	9,201	57	6.1	—8 per cent.
3	9,853	96	9.7	+44 per cent.
4	10,028	71	7.0	+4 per cent.
5	16,611	52	3.1	—53 per cent.
6	7,371	101	13.7	+104 per cent.
7	8,536	84	9.8	+46 per cent.
8	9,532	58	6.0	—10 per cent.
9	16,177	96	5.9	—11 per cent.
10	8,009	70	8.7	+29 per cent.
11	29,414	70	2.3	—65 per cent.
12	7,765	61	7.8	+16 per cent.
13	9,888	83	8.3	+23 per cent.
14	29,326	92	3.1	—53 per cent.
15	9,257	92	9.9	+47 per cent.
16	8,337	76	9.1	+35 per cent.
17	18,190	91	5.0	—25 per cent.
18	29,071	93	3.1	—53 per cent.
19	11,708	60	5.1	—23 per cent.
20	8,897	83	9.3	+38 per cent.
21	13,604	127	9.3	+38 per cent.
22	15,587	91	5.8	—13 per cent.
23	12,858	90	6.9	+2 per cent.
24	25,694	109	4.2	—37 per cent.
25	20,985	66	3.1	—53 per cent.
Total	352,387	2,005	Average 6.7	....

*The only ward that showed a change in its relative position as to cancer frequence—i. e., above or below the average—for the entire period, 1880-99, and for the second decade, 1890-99, was ward 9, which changed from a minus (—) ward for the whole period to a plus (+) ward for the second decade.

As thus indicated, nearly every ward in the region showing a concentration of dots is shown to represent a real and not merely an apparent concentration of cancer. The region showing the greatest concentration is distinctly a region occupied largely by foreigners, Germans greatly predominating, consisting of wards 15, 16, 6, 12, 13, 7, 8, 9, 10, 3 and 4. Contrast with this area of concentration (German quarter) an area of more than equal population, inhabited chiefly by native-born, consisting of wards 22, 24, 25, 17 and 18, which shows only about one-half the number of dots. The contrast is striking. The figures for the two areas are as follows:

German wards: Population, 104,753; cases, 888.

Native wards: Population, 109,527; cases, 450.

To represent the contrast even more strikingly, compare ward 24, which is one of the finest residence sections in the city, occupied chiefly by native-born, with the three wards most strongly German in their population, namely, wards 15, 16 and 6. The population of the two sections is about equal, 25,694 and 24,965 respectively, but the cancer cases in the German wards (269 cases) are about two and one-half times as many as those in the American ward (109 cases). Until the United States Census of 1900 is published, we have no exact method of estimating the proportion of foreigners and different races in the various city wards, and we have therefore been obliged to rely upon the officials of the city government for information in regard to the race distribution of population in the different wards of the city. We have no doubt, however, of the substantial accuracy of their estimates.

There is shown, then, a center of concentration of cancer in those wards in which the German element predominates. As to other classes of foreigners, we can draw no conclusions from the map distribution alone considered, as there is less tendency upon the part of other nationalities to concentrate in certain parts of the city than is shown by the Germans. There are, for instance, no distinct English, Canadian or Irish quarters in the city. The Poles, for reasons stated below, are classed with the Germans and share with them in large measure their ward distribution. There is, however, a distinct Italian quarter in the lower end of ward 19, centering in Canal street, a quarter very densely populated. This quarter shows a conspicuous absence of any concentration of dots on the map, and the ward, of which it is a part, shows a low rate (see Table II). This fact agrees with the low cancer rate in Italians shown below under

Race Distribution. That a true concentration of cancer occurs among the Germans out of proportion to their representation in population will be shown again below by other considerations, thus confirming the concentration in the German quarter shown by the map.

Aside from the relation to race, no other relation between cancer distribution and other conditions can be determined from the map distribution. There is no relation of cancer to the water courses and water front of the city, thus differing from Behla's finding at Luckau. All the wards bordering on the water front show low rates. No peculiar conditions are found in the German wards to excite suspicion, so far as we have been able to observe. It is a fact worthy of mention, however, in connection with Behla's charges against uncooked garden vegetables, that the Germans quite commonly raise a few garden vegetables and are in the habit here, as elsewhere, of eating many of them uncooked, and thus possibly contaminated by reason of some unknown conditions of nature. No special conditions of soil, however, seem to characterize the German quarter as opposed to other parts of the city.

Multiple-case Houses ("*Cancer Houses*").—As indicated on the map, 44 of the houses in which cases of death from cancer occurred represented more than one case, 41 houses having had two cases and 3 houses three cases each. Of the 2,005 deaths from cancer where the residence was known, 91, or 4.53 per cent., occurred in such houses. While we are not able to affirm that such a percentage is more than would be naturally expected, still we are somewhat inclined to this opinion, in view of the fact that Buffalo had 37,290 dwellings in 1890 and probably more than 50,000 in 1900.

An inspection of all the "cancer houses" was made and they were found in general to be one or two-story frame houses without base-

ments or cellars and only exceptionally of the class known as large tenement houses. In fact, the city contains few large tenement houses, most of the houses being small single dwellings, surrounded each by its own yard. The average number of occupants in the "cancer houses" was found to be 6.94 per house, about the same as in the city at large, which showed an average of 6.84 persons per dwelling in 1890 (U. S. Census). The same tendency shown by the cases in general is seen also in the "cancer houses" to concentrate in the German district. None of these "cancer houses" were institutions or hospitals, public or private, all such institutions being excluded from consideration.

The interval of time separating the deaths from cancer in the different "cancer houses" is shown in Table III. In almost half of the houses the interval was less than five years and in three-quarters it was less than ten years.

TABLE III.—*Classifying the multiple-case houses by the interval elapsing between the cases.*

Interval.	Number.		
1st year	4	21	36
2d year	6		
3d year	6		
4th year	3		
5th year	2		
6th year	4	15	
7th year	2		
8th year	2		
9th year	6		
10th year	1		
11th year	2	8	
12th year	3		
13th year	1		
15th year	2		
17th year	1	3	
19th year	2		
	*47		

* The difference between the number of multiple-case-houses and the intervals is due to the occurrence of triple cases in three of the houses.

In only a minority of the "cancer houses" was it possible to ascertain the relationship or lack of such between those dying of cancer in such houses. Blood relationship could be ascertained in only

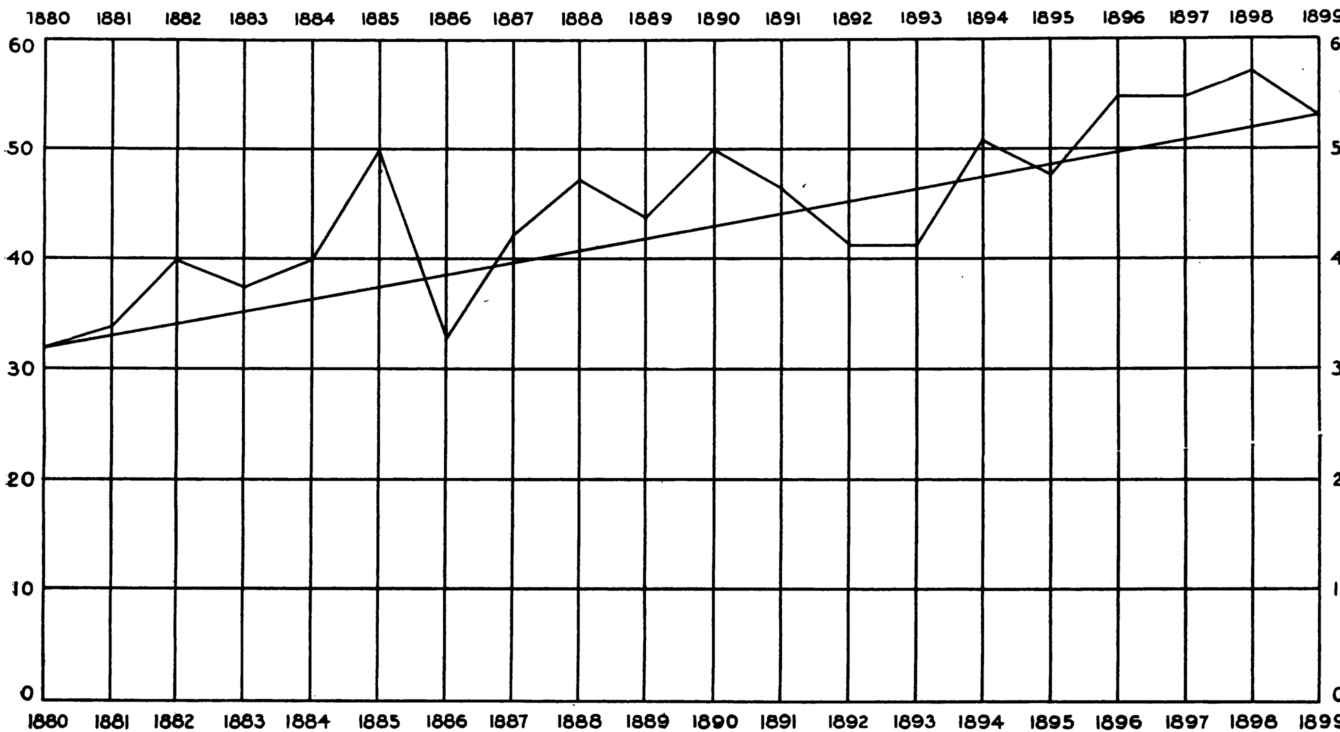
four double cases, as follows: Father and daughter, mother and daughter, father and son, and brother and sister. The second death followed the first in these four double cases respectively in the second, sixth, first and third year. Five of the eight cases were in Germans, the other three in Americans.

The relationship of husband and wife was found five times, all the ten individuals being Germans. The second death followed the first in the first, second, second, fourth and ninth year respectively.

Increased Cancer Rate.—Fig. 1 shows graphically the increasing rate of cancer mortality per 100,000 of estimated* population in Buffalo, yearly for the twenty years, 1880–1899. During this period the rate increased from 32 to 53 per 100,000 of population, or 65 per cent. This progressive increase agrees with a similar marked increase for all countries in the civilized world, and is the chief cause for alarm in the cancer problem. While tuberculosis and most other infectious diseases show a steadily decreasing mortality in different countries, everywhere cancer continues to increase year by year in the rate at which it claims its victims. After crediting the various factors that have been shown to account for an increasing cancer rate, viz., increased longevity, improved certification of death, more accurate diagnosis, etc., still there seems to be a large residue of cancer increase that cannot be accounted for by such explanations.

* The exact population was known for the years 1880, 1890 and 1900 from the U. S. census. For intermediate years it was estimated by the mathematical formula of geometrical progression, the method employed by the Registrar-General of England. This method applies strictly only to the natural increase of population by the excess of births over deaths, and not to the increase or decrease by immigration and emigration. The latter fluctuates year by year, due to temporary influences operating to increase or check immigration and emigration. Hence the curve between the end points can be regarded merely as approximately correct. Still, as there is no importance attaching to the rate for the intermediate individual years, and as merely the general rate of increase through the entire period is of interest, the plot serves its chief purpose in showing this general increase through a period of twenty years, and is therefore of almost equal value with a plot correct for all its intermediate points.

FIG. I. Showing the increasing death rate from malignant disease per 100,000 of population in Buffalo, yearly for the period, 1880–1899.



There must obviously be a limit to the operation of such factors as explanation of the continued increase of cancer. The rate of increase is too high, progressive, and general throughout the world to be anything less than real, and we believe that expert opinion is gradually reaching this conclusion.

The rate of increase in Buffalo is seen to be less marked for the second than the first decade. This is probably explained, in part at least, by the well-known falling off in immigration during the second decade as compared with the first. As will be shown below (see *Race Distribution*), the mortality rate from cancer for foreigners in general and for Germans in particular is much higher than for native-born, hence the ratio of these two general elements of the population (foreign and native-born) must be considered in drawing conclusions from the cancer rate and the change of such rate through consecutive periods of time. This important factor seems to have been previously unrecognized and neglected by writers on the cancer rates of the cities and states of the United States, where foreigners constitute so considerable a proportion of the population. The Buffalo statistics show that foreigners, as a class, are about four and one-half times more susceptible to cancer than are those of native birth, and the United States Census of 1890 showed for 28 large cities in the United States that foreigners were about three and one-fifth times more susceptible to cancer than those of native birth. That the increased cancer rate in Buffalo, from 32 to 53 per 100,000 of population from 1880 to 1899, cannot be attributed simply or even largely to an increased proportion of foreign immigrants in the population of the city is indicated by the fact that the city's foreign population increased only from 33.0 per cent. to 35.0 per cent. of the entire population from 1880 to 1890 (U. S. Census). The proportion of foreigners in 1900 has not yet been published, but will probably

show a decrease from the figure for 1890. It would be interesting and valuable to show the rate of increase of cancer per 100,000 of corresponding population separately for foreigners in general, Germans in particular, and those of native birth, but it would be possible to do so only for the census years, 1880 and 1890, and as the figures for single years for each class are relatively small, the chances of accidental variation would render such a calculation of little value.

Race Distribution.—The distribution of malignant disease according to the place of birth of those affected is shown in Table IV. The striking fact in the race incidence of cancer, shown by this table, is that individually and collectively *all foreign nationalities show a higher rate than the native-born* (United States) in proportion to representation in population.*Those of foreign birth, as a class, constitute 35.0 per

*The representation in the population of the city of the different nationalities and classes used as the basis of calculation is that shown by the U. S. census of 1890. This was chosen as the closest approximate estimation obtainable for the twenty year period, falling midway in the period. The changes occurring from 1880 to 1890 in some of the more important classes are shown in the following table, based upon the U. S. census:

	1880.	1890.	1900.
Total population	155,134	255,664	352,387
Native-born	66.9 per cent.	64.9 per cent.	Not published.
Foreign-born	33.0 per cent.	35.0 per cent.	Not published.
German	16.4 per cent.	16.6 per cent.	Not published.
Polish	0.4 per cent.	3.4 per cent.	Not published.
Irish	6.6 per cent.	4.5 per cent.	Not published.
English	2.7 per cent.	2.7 per cent.	Not published.
Scotch	0.7 per cent.	0.6 per cent.	Not published.
Canadian	3.8 per cent.	4.1 per cent.	Not published.
Italian	....	0.7 per cent.	Not published.

The census figures for 1900, not yet available, will probably show a falling off in the percentage of the foreign-born population. As a moderate increase is shown in the percentage of foreign-born during the first decade and as there is good reason for believing that a corresponding decrease will be shown for the second decade, we are probably not far amiss from the true approximation for the whole period in taking the known figures for 1890 as the basis of calculation, though in so doing we acknowledge the introduction of possible errors. Therefore, the resulting figures, representing the frequence of cancer in the different race groups compared with those of native birth, cannot be regarded as exact but only as approximate and are so treated by us in drawing conclusions from the same. The most accurate method would be to state the rate of cancer per 100,000 for each race and we regret that it is impossible to obtain data for such an estimation.

cent. of the entire population and 70.9 per cent. of the entire cancer mortality of the city, whereas, by contrast, the native-born represent 64.9 per cent. of the population of the city and only 29.0 per cent. of the cancer mortality. Hence, estimated on an equal basis of population, the death rate from cancer in the city of Buffalo is found to be 4.59 times greater for those of foreign-birth than for those born in the United States.

TABLE IV.—*Showing Distribution by Race and Race-Groups and by Sex of Malignant Tumor in Buffalo, 1880–1899.*

BIRTHPLACE.	1880–1889. Male.	1880–1889. Female.	1880–1889. Both sexes.	1880–1889. Ratio m. to f., the latter taken as 100.*	1890–1899. Male.	1890–1899. Female.	1890–1899. Both sexes.	1890–1899. Ratio m. to f., the latter taken as 100.*	1880–1899. Male.	1880–1899. Female.	1880–1899. Both sexes.	1880–1899. Ratio m. to f., the latter taken as 100.*	1880–1899. Per cent. of all cases.*	Per cent. of total population of Buffalo represented by nationalities (U. S. census, 1890).*	Ratio of frequence of malignant disease by races compared with native-born as 1.00.*
Germany	155	174	329	89	291	308	599	94	446	482	928	92	40.3 per cent.	16.6 per cent.	5.50 times 1.00 (U. S.).
United States	82	166	248	49	145	274	419	52	227	440	667	51	29.0 per cent.	64.9 per cent.	1.00 (standard of comparison).
Ireland	42	67	109	62	69	116	185	59	111	183	294	60	12.7 per cent.	4.5 per cent.	6.40 times 1.00 (U. S.).
England	12	28	40	42	29	49	78	59	41	77	118	53	5.1 per cent.	2.7 per cent.	4.27 times 1.00 (U. S.).
Canada	4	12	16	33	19	54	73	35	23	66	89	34	3.8 per cent.	4.1 per cent.	2.09 times 1.00 (U. S.).
Poland	1	3	4		28	22	50	127	29	25	54	116	2.3 per cent.	2.4 per cent.	1.52 times 1.00 (U. S.).
Scotland	4	7	11		4	13	17	30	8	20	28	40	1.2 per cent.	0.6 per cent.	4.54 times 1.00 (U. S.).
France	5	5	10		4	6	10		9	11	20				
Italy	2	1	3		6	6	12		8	7	15			0.7 per cent.	1.93 times 1.00 (U. S.).
Switzerland	2	2	4		5	1	6		7	3	10				
Russia	1	2	3		4	2	6		5	4	9				
Holland	1	2	3		3	1	4		4	3	7				
Austria		2	2		1	2	3		1	4	5				
Sweden		1	1		2	2	4		2	3	5				
Belgium	1	1	2						1	1	2				
Spain						2	2			2	2				
Norway					1		1		1		1				
Denmark						1	1			1	1				
Europe (not specified)		1	1		1	1	2		1	2	3				
Not stated	2	10	12		12	17	29		14	27	41	51	1.7 per cent.		
Total	314	484	798	64	624	877	1,501	71	938	1,361	2,299	68	100 per cent.		
Germany and Poland	156	177	333	88	319	330	649	96	475	507	982	93	42.7 per cent.	20.1 per cent.	4.81 times 1.00 (U. S.).
Europe, except Germany and Poland	70	119	189	58	129	202	331	63	199	321	520	61	22.6 per cent.		
Europe, except Germany	71	122	193	58	157	224	381	70	228	346	574	65	24.9 per cent.		
United States and Canada	86	178	264	48	164	328	492	50	250	506	756	49	32.8 per cent.		
Great Britain and Ireland	58	102	160	56	102	178	280	57	160	280	440	57	19.1 per cent.	8.0 per cent.	5.13 times 1.00 (U. S.).
All foreign countries	232	318	550	72	479	603	1,082	79	711	921	1,632	77	70.9 per cent.	35.0 per cent.	4.59 times 1.00 (U. S.).
All foreign countries, except Germany and Poland	76	141	217	53	160	273	433	58	236	414	650	57	28.2 per cent.	14.8 per cent.	4.31 times 1.00 (U. S.).

*The ratios and percentages are given for only those races that are represented by a fair number of cases.

Individually each foreign nationality shows a similar preponderance over the native-born, varying from 1.93 to 6.40. It would be unsafe to draw conclusions from these figures as to the relative susceptibility to cancer of each individual race, as the total number of cases for the various individual races is too small to warrant their trustworthy use for this purpose. However, a few races and race groups are represented by a sufficiently large number of cases upon which to base such conclusions, at least in a broad way. It is seen that the Irish show the greatest cancer rate, namely 6.40 times that of the native-born. The Germans come next with a rate of 5.50 times that of the native-born. The Scotch and English show rates of 4.54 and 4.27 respectively. The lowest rate shown by any race, excluding the Poles for reasons mentioned below, is that of 1.93 for the Italians, though the figures upon which this rate is based are too small to be more than suggestive.

In considering *race groups* we have united the Germans and Poles, as there is no satisfactory method of accurately separating them, for the reason that most of the Poles in Buffalo come from German Poland and give their nationality indifferently as German or Polish. Moreover, there are many characteristics of life common to both peoples. The Germans and Poles together, then, show a cancer rate 4.81 times that of the native-born, as compared with a rate of 4.31 for all foreigners except Germans and Poles. The Germans and Poles, therefore, show a rate in excess of all other foreigners, as a class, and are exceeded only by the Irish, who show the highest rate, namely, 6.40.

The general conclusions then are as follows: The foreign-born population of Buffalo shows a cancer rate several times greater than that of the native-born, and of the different nationalities the Irish seem to have the highest rate, the Germans and Poles the next highest rate, and the Italians the lowest rate.

In corroboration of the high cancer rate in the foreign-born as compared with the native-born, shown by the Buffalo statistics, the following table, modified from the United States Census of 1890, is shown:

Table from the United States Census, 1890, showing for 28 cities in the United States the death rates for cancer and tumor during the census year, 1890, by general nativity per 100,000 of corresponding population, and for 18 of these cities the additional distinction of certain birthplaces of mothers.

Twenty-eight cities in the United States.	Aggregate.	White.					Colored.	Birthplaces of Mothers (18 Cities).		
		Total.	Native born.			Foreign born.		United States (white).	Ireland.	Germany.
			Total.	Both parents native.	One or both parents foreign.					
Total...........	52.99	53.60	31.12	52.32	17.41	99.23	41.01	39.33	65.40	59.83

This table shows that for 28 large cities in the United States in 1890 the mortality from cancer and tumor per 100,000 of corresponding population was 31.12 for those of native birth and 99.23 for those of foreign birth, or a rate for foreigners 3.18 times that for native-born. [It also shows the remarkable and inexplicable fact that among those who were born in the United States, cancer was more than three times more frequent in those whose parents were also native-born than in those whose parents, one or both, were foreign-born!] The United States Census of 1890 unfortunately did not classify its mortality statistics by the birthplace of the deceased but by the birthplace of the mother of the deceased, and there is no way of determining for a given class, whose mothers were born in a certain foreign country, how many of such class were born in the

country of mother's birth and how many were born in the United States from such mothers. However, in so far as the mother's birthplace is a guide to the birthplace of a certain proportion of a given class and thus of the class, the above table confirms our Buffalo statistics by indicating that the Irish show a somewhat higher cancer rate than the Germans, both showing very high rates.

We have made no distinction between blacks and whites in our statistics for Buffalo, as the colored population is so small as to be insignificant.

In considering the high cancer rates of the foreign-born, we must take account of the fact that the average age and the age-periods of the foreign-born are considerably higher than those of the native-born, for cancer is a disease occurring chiefly after middle life. The amount of correction in the high cancer rates of the foreign-born on this account cannot be estimated,* but that it must be considerable is evident. However, it seems highly improbable that this factor could account for more than a fair share of the very high rates in the foreign-born, when we consider that the foreign-born in Buffalo show 4.59 times the cancer rate of the native-born and that in the 28 cities of the above table, the corresponding rate is 3.18. We apparently have, then, a real and absolute preponderance of cancer in the foreign-born over the rate in the native-born. Moreover, the rates in the foreign-born immigrant (after ample deduction for age influence) are much higher than the rates of the same nationalities in their own countries, as published in the official mortality reports of such foreign countries. It is thus shown that cancer claims not only a vastly higher percentage of victims among the foreign-born immigrants in the United States than among the native-born, but that

* The ideal method of comparison of the native-born and foreign-born rates, taking account of age differences, would be by determining for each class the rate of cancer per 100,000 of corresponding population for each age period.

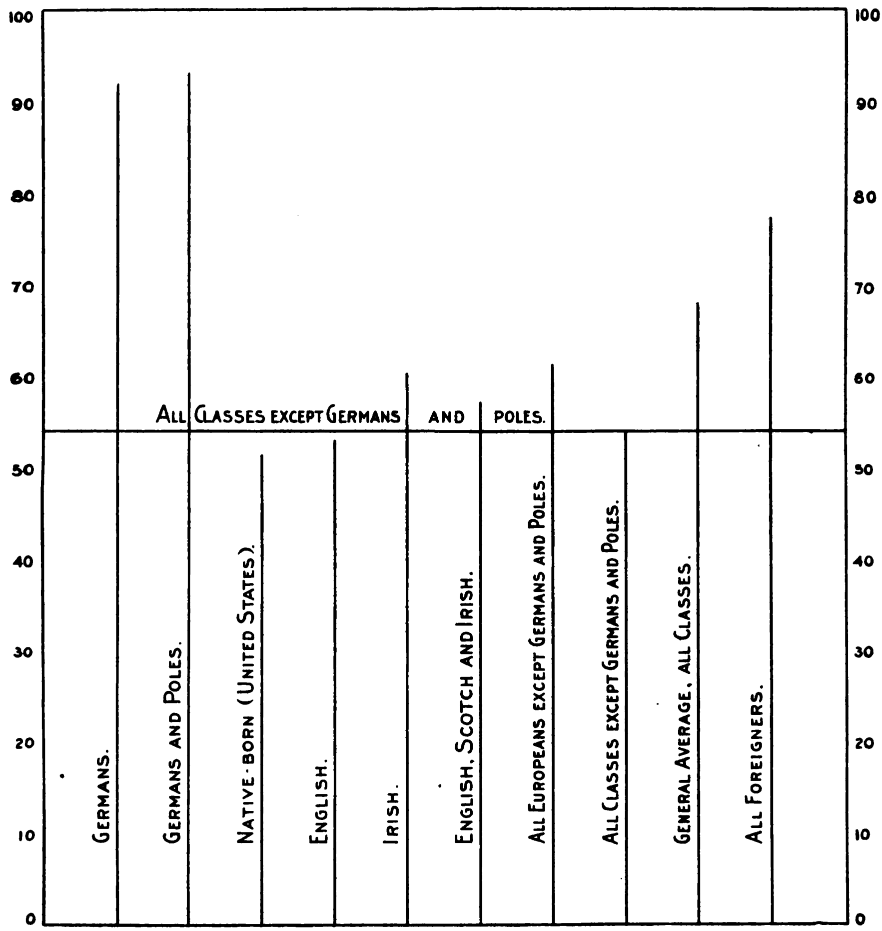
such immigrants show a similar great increase over the general rates of their kinsmen in the foreign countries from which they emigrated.

The figures and rates, above given, emphasize the importance of the general facts pointed out. The explanation of these facts is not simple. There are those, doubtless, who would argue that these facts could be brought into harmony with the Cohnheim hypothesis, or embryonic theory, of the origin of cancer, by supposing that foreign immigrants, owing to the hardships of life in a new country, exhaust their vitality and subject their organs to degenerative changes, thus laying the foundation for the growth of the hypothetical misplaced embryonic cells, which develop into cancer. But such an explanation seems strained and improbable and cannot be left unchallenged. How much more probable seems the explanation that cancer is an infectious disease and, like many other infectious diseases, claims its victims in increased ratio among those who, by the exigencies of life in the struggle against natural obstacles in a new country, are most exposed to infection?

The high cancer rate of the Germans and Poles confirms the concentration shown by the map in the German and Polish wards. The low rate among Italians also agrees with the relative freedom of the Italian quarter from cancer shown on the map.

Age Distribution.—The age distribution for the 2,299 cases of malignant disease is shown in Table V. Nothing new is shown by this table. The well-known infrequence of cancer in the early decades of life is shown. The first decade shows a higher mortality than the second, due to the greater frequence of sarcoma in the earliest years of life. The greatest mortality occurs during and after middle life, 52 per cent. of the cases occurring in the sixth and seventh decades, and 70 per cent. in the fifth, sixth and seventh decades. The mortality rate from cancer increases after middle life

FIG. II. Showing the male to female mortality, the latter taken as 100, from malignant disease for different classes of population in Buffalo, for the period, 1880–1899.



for each succeeding decade, though the absolute number of cases diminishes after the sixth and seventh decades due to the smaller number of persons living to these advanced age periods.

TABLE V.—*Age Distribution.*

AGE.	Male.	Female.	Both.	
0-9 years	12	6	18	
10-19 years	1	5	6	
20-29 years	25	19	44	
30-39 years	60	143	203	
40-49 years	152	275	427—18 per cent.	70 per cent.
50-59 years	252	357	609—26 per cent.	
60-69 years	266	332	598—26 per cent.	
70-79 years	141	181	322—13 per cent.	
80-89 years	28	39	67	
90-99 years	1	3	4	
Not stated	0	1	1	
Total	938	1,361	2,299	

Sex Distribution.—Table IV shows the sex distribution of the 2,299 cases of malignant disease generally and for each important race and race-group. Fig. II represents graphically for the entire period the number of males to females, the latter taken as 100, for several races and classes of the population. A remarkable difference of sex proportion is thus shown between the Germans and Poles on the one hand and all other classes of the population on the other. The Germans and Poles stand as a class by themselves apart from all other nationalities in showing a male rate closely approximating the female rate, 93 : 100. All other nationalities show a much lower male rate, ranging from a minimum of 51 : 100 for the native-born to a maximum of 61 : 100 for all Europeans exclusive of Germans and Poles. The common text-book statement that cancer is twice as frequent in females as in males is thus confirmed for the native-born (51 : 100) and is approximately correct for every other class except Germans and Poles.

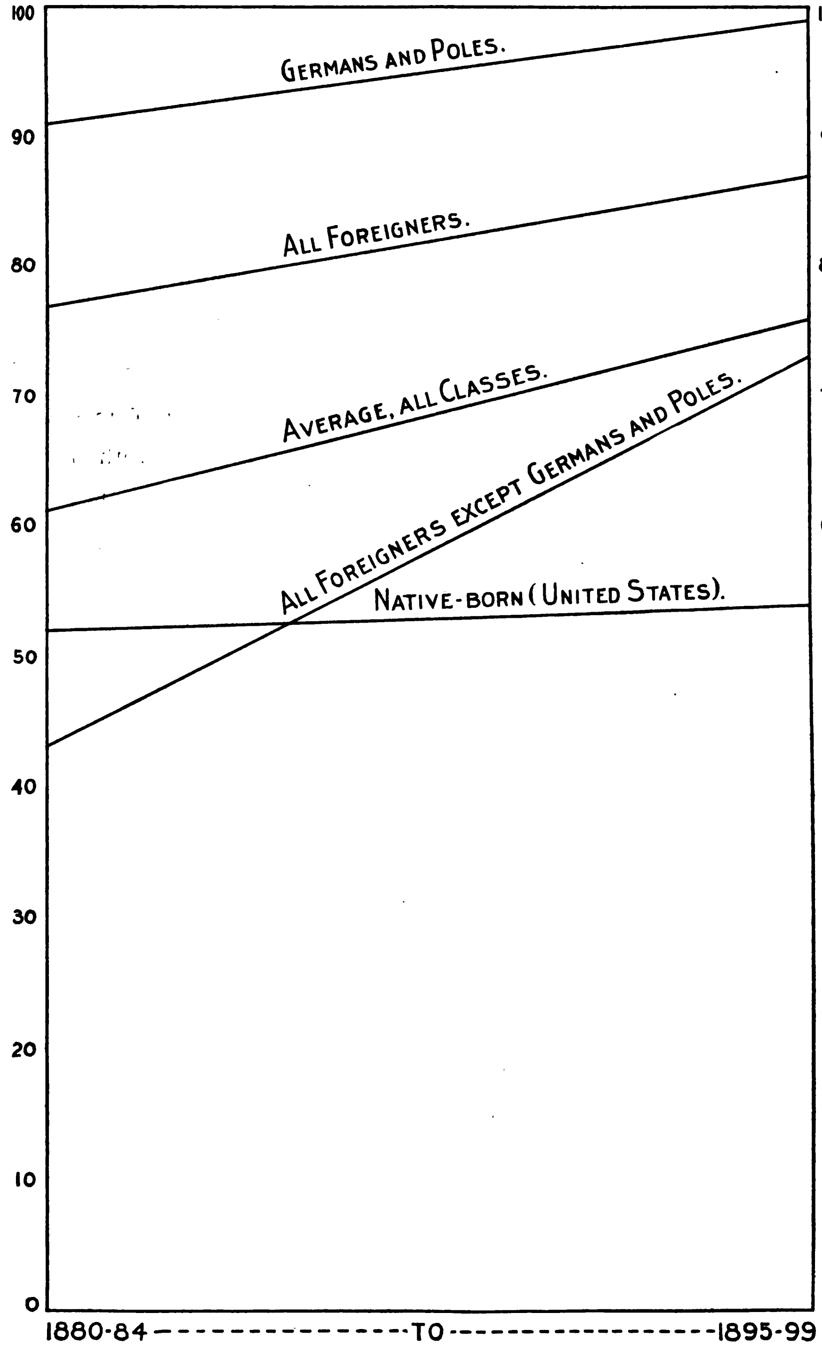
As the United States Census of 1890 did not classify its mortality statistics by race, it is not possible to make a comparison of the sex ratios of the different races for Buffalo and for the United States, as a

whole, and this can be done only for the two general classes of population, the native-born and the foreign-born. For these general classes the ratios closely agree for the United States and for Buffalo, as follows: Native-born, Buffalo, 51 : 100, United States, 53 : 100; foreign-born, Buffalo, 77 : 100, United States, 79 : 100.

We can find only one satisfactory explanation of the very high male rate in the Germans and Poles above other classes, in the fact that cancer of the stomach, which is more common in males than in females, is particularly frequent in Germans and Poles, whereas cancer of the uterus and breast in females is much less frequent among Germans and Poles than among the native-born (see *Anatomical Distribution*). The correlation of these factors with the sex ratio of cancer is apparent. That the peculiarly high male cancer rate in the Germans and Poles is not dependent upon a preponderance of males in these races in Buffalo is rendered very probable by the fact that though the Germans and Poles constitute 57.5 per cent. of all foreigners in Buffalo, the proportion of males in the foreign-born population of Buffalo (51.38 per cent.) is almost identical with the proportion of males in the entire population of the United States (51.21 per cent.).

Fig. III shows the increasing rate of male to female mortality for different races from 1880–84 to 1895–99. An actual increase in the male rate is shown for each class. The increase is marked for all foreigners, and so slight as to be almost insignificant for the native-born. An increasing male rate has been noted generally in European countries and has been attributed to increasing frequence of cancer of the stomach and internal organs in males. The very slight increase in the male rate in the native-born in Buffalo probably indicates that there has been little relative increase of cancer of the stomach in the native-born.

FIG. III. Showing the increasing proportion of male to female mortality, the latter taken as 100, from malignant di sease for different classes of population in Buffalo, from the period, 1880–1884, to the period, 1890–1899.



Anatomical Distribution.—Table VI includes a general classification of all malignant cases according to their general variety and according to whether or not the anatomical location was stated in those classed as cancer. The term cancer, as here used, includes only carcinoma and epithelioma. Table VII shows the anatomical distribution by organs of the 1,783 cases of cancer in which the site was stated, and Tables VIII and IX show the same thing respectively for those born in the United States and those born in Germany (and Poland).

TABLE VI.—*Classification of cases of malignant disease according to general variety, etc.*

	1880.		1881.		1882.		1883.		1884.		1885.		1886.		1887.		1888.		1889.		TEN YEARS, 1880–1889.	
	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.
Cancer, anatomical location stated	11	15	10	21	12	26	2	5	22	22	32	46	13	41	27	52	30	39	32	39	191	306
Cancer, anatomical location not stated	3	20	9	12	8	21	24	35	16	14	6	8	6	3	4	5	13	18	11	14	100	150
Malignant tumor, variety not stated	....	....	1	2	1	1	....	....	....	1	2	5	3	1	3	2	3	5	3	4	16	21
Sarcoma	1	....	1	....	....	....	....	1	1	1	....	1	2	1	....	....	....	1	2	2	7	7
Totals	15	35	21	35	21	48	26	41	39	38	40	60	24	46	34	59	46	63	48	59	314	484
Totals	50		56		69		67		77		100		70		93		109		107		798	

	1890.		1891.		1892.		1893.		1894.		1895.		1896.		1897.		1898.		1899.		TEN YEARS, 1890–1899.		TWENTY YEARS, 1880–1899.		
	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Both sexes.
Cancer, anatomical location stated	30	74	36	59	27	61	45	57	62	72	47	75	71	86	73	89	72	95	63	92	526	760	717	1066	1,783
Cancer, anatomical location not stated	6	8	3	12	4	6	2	5	3	4	....	5	2	4	....	2	2	3	1	8	23	57	123	207	330
Malignant tumor, variety not stated	1	2	4	6	1	2	....	....	....	....	3	1	3	2	1	2	4	4	2	3	19	22	35	43	78
Sarcoma	4	4	2	4	8	3	5	3	5	3	10	4	5	....	5	4	4	7	8	6	56	38	63	45	108
Totals	41	88	45	81	40	72	52	65	70	79	60	85	81	92	79	97	82	109	74	109	624	877	938	1361	2,299
Totals	129		126		112		117		149		145		173		176		191		183		1,501		2,299		2,299

TABLE VII.—*Anatomical Location—all races—in all cases of cancer in which the location was specified.*

ORGANS		Number of Times Involved.			Per Cent. of Cases Showing Such Involvement.		
		Male.	Female.	Both.	Male.	Female.	Both.
Genital Organs	Male	10	....	10	1.3	....	0.5
	Female: Uterus	....	352 } 370	352 } 370	....	33.0 } 34.7	19.7 } 20.7
	Female: Other	....	18	18	....	1.7	1.0
Breast		4	155	159	0.5	14.5	8.9
Urinary Organs	Kidney	3 } 16	7 } 14	10 } 30	0.4 } 2.2	0.6 } 1.3	0.5 } 1.6
	Bladder	13	7	20	1.8	0.6	1.1
Upper Alimentary Canal	Mouth	6 } 70	2 } 17	8 } 87	0.8 } 9.7	0.1 } 1.5	0.4 } 4.8
	Tongue	17	3	20	2.3	0.2	1.1
	Jaw	18	4	22	2.5	0.3	1.2
	Throat	29	8	37	4.0	0.7	2.0
Middle Alimentary Canal	Oesophagus	30 } 372	2 } 272	32 } 644	4.1 } 51.8	0.1 } 25.5	1.7 } 36.1
	Stomach	342	270	612	47.6	25.3	34.3
Lower Alimentary Canal	Intestine	37 } 89	41 } 87	78 } 176	5.1 } 12.4	3.8 } 8.1	4.3 } 9.8
	Rectum	52	46	98	7.2	4.3	5.4
Abdominal Organs (not otherwise included)	Liver	87 } 129	124 } 168	211 } 297	12.1 } 17.9	11.6 } 15.7	11.8 } 16.6
	Other	42	44	86	5.8	4.1	4.8
Thoracic Organs	Heart	... } 3	1 } 7	1 } 10	... } 0.4	0.0 } 0.6	0.0 } 0.5
	Lung	3	6	9	0.4	0.5	0.5
Head and Face		37	17	54	5.1	1.5	3.0
Neck		26	3	29	3.6	0.2	1.6
Extremities		11	6	17	1.5	0.5	0.9
Other Locations		....	5	5	....	0.4	0.2
Total Organs		767	1,121	1,888	....	....	....
Total Number of Cases		717	1,066	1,783	....	....	....

TABLE VIII.—*Anatomical Location—native born (United States)—in cases of cancer in which the location was specified.*

ORGANS.		Number of Times Involved.			Per cent. of Cases Showing Such Involvement.		
		Male.	Female.	Both.	Male.	Female.	Both.
Genital Organs	Male	3	....	3	2.0	....	0.6
	Female: Uterus	....	149 } 159	149 } 159	....	44.6 } 47.6	30.7 } 32.8
	Female: Other	....	10	10	....	2.9	2.0
Breast		1	57	58	0.6	17.0	10.9
Urinary Organs	Kidney	1 } 3	... } 2	1 } 5	0.6 } 2.0	... } 0.5	0.2 } 1.0
	Bladder	2	2	4	1.3	0.5	0.8
Upper Alimentary Canal	Mouth	1 } 17	... } 5	1 } 22	0.6 } 11.3	... } 1.4	0.2 } 4.5
	Tongue	3	2	5	2.0	0.5	1.0
	Jaw	8	1	9	5.3	0.2	1.8
	Throat	5	2	7	3.3	0.5	1.4
Middle Alimentary Canal	Oesophagus	4 } 60	... } 46	4 } 106	2.6 } 40.0	... } 13.7	0.8 } 21.9
	Stomach	56	46	102	37.3	13.7	21.0
Lower Alimentary Canal	Intestine	10 } 28	9 } 23	19 } 51	6.6 } 18.6	2.6 } 6.8	3.9 } 10.5
	Rectum	18	14	32	12.0	4.1	6.6
Abdominal Organs (not otherwise included)	Liver	18 } 32	29 } 45	47 } 77	12.0 } 19.3	8.6 } 13.4	9.7 } 15.9
	Other	14	16	30	9.3	4.7	6.1
Thoracic Organs	Heart	....	... } 5	... } 5	....	... } 1.4	... } 1.0
	Lung	....	5	5	....	1.4	1.0
Head and Face		10	4	14	6.6	1.1	2.8
Neck		3	....	3	2.0	....	0.6
Extremities		5	2	7	3.3	0.5	1.4
Other Locations		....	4	4	....	1.1	0.8
Total Organs		162	352	514	....	....	....
Total Number of Cases		150	334	484	....	....	....

TABLE IX.—*Anatomical Location—Germans and Poles—in cases of cancer in which the location was specified.*

ORGANS.		Number of Times Involved.						Per Cent. of Cases Showing such Involvment.					
		Male.		Female.		Both.		Male.		Female.		Both.	
Genital Organs — Male			2		....		2		0.5		....		0.2
Genital Organs — Female	Uterus	....		95	99	95	99	....		23.5	24.5	12.4	12.9
	Other	....		4		4		....		0.9		0.5	
Breast			3		44		47		0.8		10.9		6.1
Urinary Organs	Kidney	1	7	1	4	2	11	0.2	1.9	0.2	0.9	0.2	1.4
	Bladder	6		3		9		1.6		0.7		1.1	
Upper Alimentary Canal	Mouth	1	27	1	4	2	31	0.2	7.4	0.2	0.9	0.2	4.0
	Tongue	3		....		3		0.8		....		0.3	
	Jaw	6		....		6		1.6		....		0.7	
	Throat	17		3		20		4.6		0.7		2.6	
Middle Alimentary Canal	Oesophagus	22	214	1	145	23	359	6.0	58.9	0.2	35.9	3.0	46.8
	Stomach	192		144		336		52.8		35.7		43.8	
Lower Alimentary Canal	Intestine	16	36	22	36	38	72	4.4	9.9	5.4	8.9	4.9	9.3
	Rectum	20		14		34		5.5		3.4		4.4	
Abdominal Organs (not otherwise included)	Liver	43	60	51	76	97	136	11.8	16.5	13.3	18.8	12.6	17.7
	Other	17		22		39		4.6		5.4		5.0	
Thoracic Organs	Heart	....	2	....		....	2	....	0.5	....		....	0.2
	Lung	2		....		2		0.5		....		0.2	
Head and Face			15		7		22		4.1		1.7		2.8
Neck			13		2		15		3.5		0.4		1.9
Extremities			5		3		8		1.3		0.7		1.0
Other Locations		....		....		....		....		....		....	
Total Organs			384		420		804	....		....		....	
Total Number of Cases			363		403		766	....		....		....	

The striking facts shown by these tables are the high rate of cancer of the stomach in the Germans and Poles (43.8 per cent.) compared with those of native birth (21.0 per cent.), and on the other hand the low rate of cancer of the uterus and breast in females born in Germany and Poland (34.4 per cent.), compared with females born in the United States (61.6 per cent.). The correlation of these factors with the sex ratio for the two races has already been noted. As the sex ratio of the Germans and Poles differs widely from that of all other nationalities, it is probable that other foreign races in general may be classed with the native-born, as opposed to the Germans and Poles, in showing also a low rate of cancer of the stomach and a high rate of cancer of the uterus and breast. This is probable, but cannot be positively affirmed, as the total number of each other foreign race in our statistics is not sufficiently large to warrant us in making tables of anatomical distribution by race and in drawing conclusions from them.

The Germans and Poles, then, stand out in sharp contrast with the native-born and probably other foreigners in showing a remarkably high rate of stomach involvement and a correspondingly low rate of involvement of the uterus and breast. Cancer of the stomach relatively to cancer of the other organs, was 2.08 times more frequent among Germans and Poles (43.8 per cent.) than Americans (21.0 per cent.). As cancer in general was 4.81 times more frequent in Germans and Poles than Americans (see above), cancer of the stomach was therefore 10.00* times more frequent in a given number of Germans and Poles than in the same number of Americans in the city of Buffalo.

* As the rate 4.81 is subject to some reduction on account of the higher average age of Germans and Poles than Americans (see above), so also the rate 10.00 must be proportionately reduced for the same reason.

Such a relative frequence of cancer of the stomach in the Germans (and Poles) compared with the Americans is remarkable and requires a careful investigation of its cause. As the United States Census of 1890 did not classify by race (birthplace), we were unable to compare the high rate of stomach involvement in the Germans in Buffalo with the rate for the Germans in other American cities. We have also been unsuccessful in our efforts to obtain official German statistics and thus to compare the rate of cancer of the stomach for Germans in Buffalo with the rate for Germans in Germany. A careful personal search at the Surgeon-General's Library in Washington for such statistics proved fruitless. We are therefore left to deal with the rates for Buffalo only, unable to compare them with the rates for other American cities and for Germany. A high rate of stomach involvement is shown by both males and females among the Germans, indicating the participation of each sex in the conditions operating to elect the stomach as the seat of invasion by the cancerous process. The male, however, always predominates in all races in the rate of stomach involvement in cancer.

What significance has the remarkable frequence of cancer of the stomach among Germans in the question of the nature and origin of cancer? The coarseness and quantity of the German's diet might be claimed perhaps to account for some increase of stomach involvement on the embryonic theory or on the theory of irritation, but such simple factors seem insufficient to explain the high figures that we have shown. The parasitic theory here again seems to harmonize best with the facts and to find strong support in them. Does it not seem likely that the stomach is the seat of cancer invasion because it is directly infected by contaminated food and that the peculiar diet of the Germans is more subject to such contamination than the food of Americans or other people? In this connection

it is well to recall the observations of Behla at Luckau and the suspicion he entertained against raw uncooked garden vegetables as the carrier of cancer infection. In the cancer suburb of Luckau, also, as well as among the Germans dying of cancer in Buffalo, cancer of the stomach and liver predominated. The apparent relation at Luckau between cancer and the location of a foul ditch is lacking in Buffalo to account for the possible contamination of the garden vegetables.

If the German's stomach is far more exposed to infection than other organs, we have at least a partial explanation of the low rate of cancer of the uterus and breast in Germans. The lower rate of cancer of the uterus and breast in German than in American women seems to us to be a weighty argument against the embryonic and the irritation theories, as it is well known that the birth rate and habit of nursing at the breast are greater among the Germans than the native-born, and therefore, if these theories were correct, cancer ought to be more frequent rather than less frequent in these organs in Germans because of their relatively greater use and exhaustion. The reverse is shown to be the fact.

The special facts that we have found in the peculiar cancer distribution in Buffalo may be due partly to local conditions that may not be found entirely similar in other American cities and towns, and hence it may be that the special relations of cancer to race, sex, etc., found to exist in Buffalo, may not be entirely confirmed elsewhere. Special conditions will undoubtedly be found in each city that will determine the special local peculiarities of cancer distribution, and we believe that the labor and time spent in studying the local conditions influencing cancer distribution in different places will be repaid by results commensurate with the task involved and perhaps of great import to the successful direction of the attack against the cause of this scourge of humanity.

Summary.—We may briefly summarize the principal facts and results of our study, as follows:

(1) The house distribution of cancer on the map shows an area of marked concentration in the German wards. No other relation than that of race can be determined to exist between this area of concentration and local conditions.

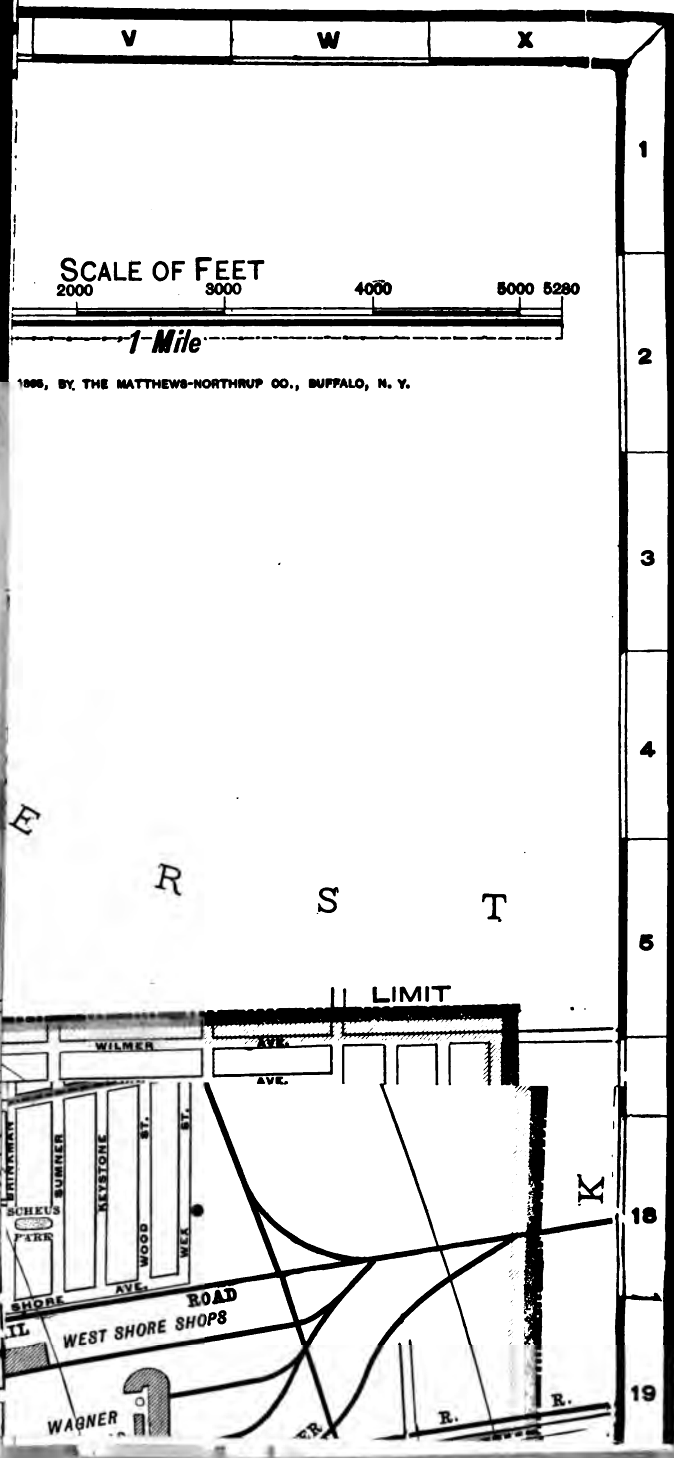
(2) That there is a real relation between this local concentration and race (German) is further indicated by the race table, which shows that cancer is many times more frequent among the foreign-born and particularly the Germans than the native-born. The latter fact is also verified by the United States census for 28 large cities. The cancer rate of foreigners, in general, was 4.59 times the rate for the native-born and the corresponding rate for Germans (and Poles) was 4.81.

(3) The Germans (and Poles) were further specially distinguished from other classes by the high rate (43.8 per cent.) of involvement of the stomach, 2.08 times the rate (21 per cent.) shown by the native-born. Cancer of the stomach, therefore, was 10 times more frequent in the Germans (and Poles) than in the native-born in Buffalo, for equal numbers of each. Such high figures seem hard to explain on the embryonic or irritation theories and tend to support the parasite theory of cancer, by supposing that the peculiar diet of the Germans is more liable to contamination with the parasite of cancer than the more ordinary diet of other classes. Cancer of the uterus and breast in Germans (and Poles) was correspondingly low, being hardly more than half as frequent as in the native-born. This fact seems to be a further important argument for the parasitic as opposed to the embryonic or irritation theories, considering the fact that the birth rate and the habit of nursing at the breast (conditions predisposing to degeneration of these organs) are greater among Germans than native-born women.

(4) The ratio of males to females, the latter taken as 100, was 93 for Germans (and Poles) and from 51 (native-born) to 61 (all Europeans except Germans and Poles) for all other races and classes. The high German male rate is probably directly dependent upon the high rate of cancer of the stomach (especially in males) and the low rate of cancer of the uterus and breast (females) found to characterize the Germans as opposed to other races.

For all classes the ratio of males to females was found to have risen during the twenty years covered by the investigation. This rise was very slight for the native-born.

(5) An increase in the general cancer rate from 32 to 53 per 100,000 of population (65 per cent.) took place from 1880 to 1899. A similar increase has been shown in all countries. This increase is thought to be partly real and not entirely apparent. The rate of increase is shown to depend in part at least upon changes in the proportion of the foreign-born, because the cancer rate in the foreign-born is so much higher than in the native-born.



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FOURTH ANNUAL REPORT

CANCER LABORATORY

New York State Board of Health

GRATWICK RESEARCH LABORATORY
UNIVERSITY OF BUFFALO

For the Year 1902-3

FOURTH ANNUAL REPORT

OF THE WORK OF THE

CANCER LABORATORY

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Conducted at the

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For the Year 1902-3

TRANSMITTED TO THE LEGISLATURE FEBRUARY 1, 1903

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1903

CONTENTS.

REPORT OF THE DIRECTOR.

BUFFALO, N. Y., *February* 1, 1903.

DR. DANIEL LEWIS, *State Commissioner of Health, Albany, N. Y.:*

Sir.—I have the honor herewith to transmit my own report as executive head of the State Cancer Laboratory, and those of my colleagues, pertaining to the work done there during the past year. The staff of the Laboratory at present consists of the following:

Dr. Harvey R. Gaylord	Pathologist.
Dr. H. G. Matzinger	Bacteriologist.
Dr. G. H. A. Clowes	Chemist.
Prof. Gary N. Calkins	Consulting Biologist.
Alice G. Owen	Assistant.
F. S. Low	Assistant in Photo-chemistry.
E. W. Jeffcott	Assistant Chemist.
Clara A. Maclay	Secretary.
F. A. Payne	Janitor.
Fred Tepe	Laborer.
M. Weber	Laborer.

Expenses of Conducting the Laboratory for the Period from February 1, 1901, to September 30, 1902.

1901.	Equipment.	Stock and material.	Sundry expense.	Salaries.	Total.
February	$241 35	$56 04	$64 95	$806 66	$1,169 00
March	33 80	73 86	39 13	786 66	933 45
April	105 55	77 70	96 67	861 66	1,141 58
May	48 50	72 77	104 58	841 66	1,067 51
June	....	....	....	841 66	841 66
July	84 10	118 21	59 42	528 32	790 05
August	7 16	26 71	62 81	333 33	430 01
September	....	....	....	333 33	333 33
October	53 25	39 57	18 53	1,141 33	1,252 68
November	1 68	24 51	23 50	736 66	786 35
December	46 34	31 73	190 27	676 66	945 00
1902.					
January	2 06	19 41	84 23	676 66	782 36
February	....	16 21	203 07	736 66	955 94
March	333 42	76 29	119 89	746 66	1,276 26
April	80 36	240 20	126 31	878 36	1,325 23
May	103 55	60 63	213 29	869 99	1,247 46
June	90 93	83 68	131 45	869 99	1,176 05
July	488 51	59 54	132 75	786 66	1,467 46
August	3 35	27 35	272 82	786 66	1,090 18
September	165 76	245 12	248 82	553 33	1,213 03
	$1,889 67	$1,349 53	$2,192 49	$14,792 90	$20,224 59

It will be noticed that this period covers twenty months, and that the entire expense for this time has been $20,224.59.

The bills for each month are audited separately by myself, are sent to you for your revision, and then go to the Governor for his signature before the Comptroller remits the amount required.

The deaths from cancer in New York State for the year ending December 1, 1902, as taken from the Bulletin of the State Department of Health, have numbered 4,984. Taken by months the statement is as follows:

Deaths from Cancer in New York State Year Ending December 1, 1902.

December, 1901	442
January, 1902	384
February, 1902,	375
March, 1902	406
April, 1902	439
May, 1902	501
June, 1902	411
July, 1902	434
August, 1902	443
September, 1902	314
October, 1902	416
November, 1902	419
	4,984

The reports of Drs. Gaylord, Calkins, Clowes, Matzinger and Lyon, herewith transmitted, will be an excellent indication of the character and the amount of work done under State auspices in this institution. A very brief outline of the general character of the work may not be amiss, and would be as follows: During the past months work has been done upon the yeasts, which we for a long time suspected to be actual parasites of cancer, until the subject was fairly exhausted and these suspicions considered to be unfounded.

This work was done with various cultures of yeast and with serums, and was followed out until it appeared that yeasts were not concerned, at least in the production of cancer. Since then attention has been given mainly to the protozoa, which are now the subjects of a very extended and searching inquiry. This is particularly true of the Plasmodiophoræ. These are known to produce tumor formation in plants, and there is constantly increasing evidence that they or some allied protozoan forms are concerned in the production of cancer. Dr. Matzinger, who has not made a separate report, has cooperated with Drs. Gaylord and Clowes in working with this organism. A very suggestive paper by Professor Calkins is also included.

Our work at present is conducted along three principal lines and in three laboratories—the pathological, the chemical, and the bacteriological—using this last term in its broader sense and meaning thereby that bacteriological methods are being applied, so far as they are applicable, to the study of other minute forms of life. That this work may go on to best advantage there must be the heartiest cooperation between these various departments, while methods and results are so dovetailed, so to speak, that it is impossible to say that the head of one department can concern himself with one solitary phase of the subject. I am glad to be able to say that this correlation of the work goes on here in the best of spirit and with the happiest of results, and that it seems to be leading up to discoveries of value and the establishment of facts of the greatest importance.

In a general way I may say that the principal work now carried on in the chemical laboratory relates to metabolism in its broadest possible sense—from that in the individual cell to that in the body at large—with a view of discovering if possible the nature of the perverted metabolism now so generally recognized in connection with cancerous disease. So much, however, has to be established more definitely regarding these changes under normal conditions before we attempt to estimate the abnormal that the work necessarily makes slow progress. In fact it is true of all the work done in this Laboratory that we have had to deal with such novel or hitherto unsolved problems on every hand that it has taken a great deal of time to be

able to approach them with any definite amount of fundamental knowledge.

This is particularly true with regard to the protozoa. There is not a practicing physician in the United States who has anything more than a rudimentary knowledge of this subject, and yet the question of cancer has become more and more a biological problem. Being thus confronted with questions of the greatest medical interest which yet could not be at present solved by medical men as such, we have added to our corps, with your approbation, Prof. Gary N. Calkins of Columbia College, who joins us as consulting biologist. He is certainly the best qualified authority on the subjects which here most interest us to be found in this country, and we look for large benefit to accrue from his advice and experience.

The publication in our last annual report, and elsewhere, of Dr. Gaylord's researches aroused, as was to be expected, considerable criticism from various directions, most of all from those least conversant with the subject. Dr. Gaylord spent some weeks last fall in Europe (without extra expense to the Laboratory) in comparing results with those of the most eminent European workers in this direction. While each reader of his present report will gather therefrom that the statements previously made have to be but little, if at all altered to accord with the present state of our progress, it is with pleasure that I assure you that from various sources, public and private, I find that the sentiment is everywhere growing that this work is conducted on proper lines, and that its results as already published constitute a very distinct advance and give very great promise. Were this the place in which to become controversial one might easily go into an animated discussion and point out the baseless character of most of the criticisms which have been directed at it. I feel, however, that it is at least due to all concerned to say that the views enunciated in our previous reports have become more and more widely accepted and corroborated.

An important part of our work is also the critical study and condensation of the special literature bearing upon it. We are gathering a library of such literature as fast as our means will permit, and we endeavor to let nothing of importance in the world's literature pass

unnoticed. You will readily see that in this effort alone not a little time has to be expended.

A very important part of our work during the past year has been the effort to determine something of the real value of the Roentgen or X-rays in the treatment of cancer. Generous friends of the Laboratory have contributed an exceedingly elaborate outfit for this purpose which has been set up in the Buffalo General Hospital and is in almost constant use there. To this feature of the subject I have mainly devoted myself. I feel that this is hardly the time or place in which to write an elaborate paper on this subject. The medical journals of late have been full of such papers and the topic has quite lost its novelty, but what has been needed in my estimation is a prolonged study based on a large number of cases and watched for a sufficient length of time in order that one's judgment may be ripened and his expressions on the subject thereby made of value. Recently a large Finsen light apparatus has been added to our hospital equipment, and I am now experimenting with a more portable apparatus for applying the ultra-violet rays for this same purpose. With this I have as yet had too little experience to justify any statement whatever, although the reports which come to us of its use abroad are mostly favorable; but with regard to the X-rays, I am quite prepared to say that in certain cases and within certain limits they offer the most helpful means for relief of pain and favorably influencing or retarding malignant growths that we at present are familiar with.

I do not mean by this to report to you that X-rays will certainly cure any kind of cancer, but I am willing to go so far as to say that certain varieties of superficial cancer have been apparently cured, and that in many instances remarkable relief has been afforded and remarkable changes witnessed. A spirit of conservatism, which I am sure you will consider wise, should prevent any more optimistic statement than this at present. It is proposed to continue these clinical investigations, upon which a more detailed report may be expected later.

The needs of our Laboratory for the ensuing fiscal year are not essentially different than those of the past. We certainly need every person now connected with the staff in order that the work may go

on, and the expenses bid fair to be about the same as before. I would like to renew the statements previously made—that the State is saved all expense in this investigation save the actual outlay of its conduct, since the University of Buffalo, through the generosity of Mrs. Gratwick and of other friends, has provided the building and most of the equipment. Consequently there is no rent to be paid.

It is an important part of our work that we should feel at liberty to employ special talent for any special line of investigation which may seem to promise an adequate return. I do not feel therefore that it would be just to ourselves and the importance of the work we are doing to ask for anything less than $15,000 for the ensuing year; i. e., the same amount which we have had previously at our command.

In conclusion I want to express our appreciation of the uniform courtesy and sympathy with which our efforts have been received by yourself and by those in authority. From yourself and from my colleagues in the Laboratory I have had always the kindest assistance and the heartiest cooperation, and I am glad at this time and in this place to record that fact and to express my grateful appreciation thereof.

ROSWELL PARK.

February 1, 1903.

ON THE PRESENT STATUS OF THE INVESTIGATION INTO THE ETIOLOGY OF CANCER BY THE CANCER LABORATORY OF THE NEW YORK STATE BOARD OF HEALTH, UNIVERSITY OF BUFFALO.

By Harvey R. Gaylord, M. D.

In the third annual report from this Laboratory the writer published a series of experimental investigations and observations which led to the conclusion that there was strong evidence of the presence of an organism in carcinomatous material. The first reference made to experiments which indicated the presence of an organism was in January, 1899, before the Medical Society of the State of New York in Albany. The suspected organisms were first observed in peritoneal fluid, where they appeared as hyaline, pale yellowish-green bodies, varying in size from slightly larger than a micrococcus to a size nearly as large as a red blood corpuscle. The smaller forms of these bodies were without structure. In the larger the suggestion of a nucleus was present. The observer incubated an uncontaminated preparation and observed the same field at repeated intervals for a period of four weeks. During this period certain of the smaller forms which were definitely located were observed to increase in size, ultimately develop what appeared to be a capsule, and terminate by dividing into numbers of small, hyaline bodies, closely resembling the original appearance. A portion of the peritoneal fluid thus obtained was injected into guinea pigs. One of these after a short period was killed and multiple nodules which, on microscopic examination, appeared to be rapidly growing adenomata or adenocarcinomata, were found in the lungs. Attempts to stain the hyaline bodies were unsuccessful until a method of pouring the peritoneal fluid into Hermann's fluid was employed, when it was found that they could be stained with a nuclear stain (iron hæmatoxylin).

These bodies were treated with osmic acid and a large proportion of them were found to resist the blackening of osmic. Peritoneal fluid, cancer mush, dried and undried lymph nodes, were injected into animals and large numbers of similar hyaline bodies were detected in the peritoneal fluid of the animals, in the circulation, and in hardened sections of the enlarged lymph nodes. From the suggestion obtained by the appearance of hyaline bodies in the blood of inoculated animals the observer examined the blood in living cachectic cancer patients and detected the presence of small, actively moving amœboid bodies, which were compared with those observed by Pfeiffer and Reed in vaccine and variola, and which, the writer was inclined to believe, represented an amœboid form of the organism found in peritoneal fluid and cancer scrapings in man. A comparison was drawn between the appearence of the hyaline bodies and those described in vaccine and the pustules of variola. An investigation of a number of cases of cancer showed the presence within the cells of what are often referred to as "Plimmer's bodies," which have been most accurately described by that author. These bodies were found to be present in a large proportion of all cases investigated. A relation between these bodies and the extra-cellular, hyaline forms found in carcinoma, known as "Russell's bodies," was indicated, as well as the similarity in appearance of the so-called "Plimmer's bodies" and the so-called "vaccine body" obtained by inoculation of the cornea with vaccine. Intra-cellular, hyaline forms somewhat resembling the so-called "Russell body," and likewise resembling certain forms of the vaccine body, were also shown. The supposed resemblance of the so-called "Plimmer's bodies" to yeasts was considered and rejected. A number of animals inoculated with cancerous material died, after a period of time approximating fifty days, with marked cachexia and with enlarged lymph nodes. In the lymph nodes of these animals hyaline forms closely resembling those found in the fresh cancerous material were observed. The development of the cachexia in these animals was compared by the writer to the terminal process of cancer in man.

Our views regarding the possibility of an extra-cellular form of a parasite in cancer have been repeatedly misinterpreted by writers

reviewing our statements. It has been stated that our observations must of necessity be incorrect, inasmuch as the nature of the cancerous process is supposed to preclude the possibility of a parasite being present except in some symbiotic relation to the cancerous epithelium. It has at no time been our belief that, if the amœboid bodies described by us represented a phase of the cancer parasite, in this phase the organism could be capable of producing reinfection. From what is known of protozoa, especially what is known of Plasmodiophora Brassicæ in the plant, it is possible for an organism to be capable of infection of specific elements of the economy in one stage of its cycle only, and having passed into a second phase become incapable of reinfection without the interposition of an ectogenous cycle, in most cases in an intermediary host. In this connection a foot-note which we added to our article as it appeared in the report to the Legislature, submitted April 15, 1901, will express our point of view at that time:

As the editorial comment upon the above paragraph, as it appeared in the *American Journal of the Medical Sciences,* shows evident misinterpretation of the writer's meaning, he has deemed it advisable to give the wording a more specific character. He has carefully avoided any theoretical deductions and has merely recorded observations as they were made in the Laboratory, with the intention of describing all of the experiments in detail in future publications. One evident misinterpretation credits the writer with the belief that cancer is a general and not a local disease. He trusts that those who will reread that portion of the article as it appeared in the *American Journal* will see that no deduction of this sort is warrantable. Cancer unquestionably begins as a local infection of the epithelium and at some stage of the disease, yet undetermined, the organisms apparently find their way into the general circulation, and, as stated above, after death can be found in all the organs of the cadaver. The exact role which the organisms play when in the peripheral blood is naturally undetermined. It is even fair to assume, from what is known of similar organisms, that they are entirely passive. A number of the protozoa which infect the blood of the lower animals produce very slight disturbance, and it is highly probable that the significance in this case is of no greater importance than showing the general distribution of the parasites in the later stages of the disease. It is our belief that the termination of fatal cancer cases bears some relation to the general distribution of the organisms, but we have carefully avoided all speculations as to the significance of the above observations.

Since the publication of our article in the May number of the *American Journal* and in the form of the Third Annual Report of this Laboratory a series of investigations relating to the amœboid form of the blood platelet have appeared, which throw much new light

upon the subject of amœboid bodies in the blood of human beings and animals. For this reason it is desirable for us to review the evidence as it stands.

The bodies which we observed were first found in peritoneal fluid in a case of cancer. The description, as given in our previous article, is as follows: "A careful microscopic examination was likewise made of the peritoneal fluid. It was found to contain a few blood corpuscles and some pale, spherical bodies, in size varying from 2 to 10 micromillimeters. They were homogeneous, of a pale, yellowish-green color, and at first were mistaken for fat droplets, although on closer examination their refractive index was seen to be too low.

"When treated with osmic acid they failed to give the black reaction which characterizes fat. Attempts to stain them were partly successful, and it was found that with cover slips fixed by heat, although the bodies were greatly deformed by the process, a certain number of them could be stained with carbol-thionin or the usual aniline dyes. Some of these bodies, though not very numerous, contained granular material which showed marked Brownian movement. The tubes were examined from day to day and we were able to demonstrate that these spherical bodies gradually increased in size, became more indefinite, gradually lost their yellowish-green color. As they increased in size they apparently became more fluid and commonly sent out pseudopods and long projections. Fine, colorless granules appeared in the protoplasm, and in some a delicate nucleus could be made out."

An examination was then made of a number of cases of carcinoma in the last stages, with the result that similar bodies were detected.

"In one case of general carcinosis small amœboid bodies were found in the blood immediately after it was withdrawn from the patient. These conformed very closely in appearance to similar bodies described by Pfeiffer and Reed in the blood of vaccinated children and monkeys. The younger forms of the organism may likewise be found in the peripheral blood of the animals after inoculation with cultures* or carcinomatous material."

*The term "culture" is here used to indicate culture in the biological sense. We observed these amœboid bodies increasing in size and passing through what appeared to be a portion of a cycle. Cultivation in the bacteriological sense of a protozoon is, of course, impossible.

On turning to the observations of Reed* referred to, it will be seen that he observed in the blood of vaccinated children, calves and monkeys and in the blood of patients suffering from variola, *first,* granular, amœboid bodies having a diameter about one-third that of a red blood cell. These appeared during the active stage of vaccinia and disappeared with the decline of the local inflammation. A body of like appearance, granulation and size may occasionally be found in the normal blood of monkeys and children. *Second,* pale, amœboid bodies containing a few dark, pigment-like granules are present in the blood from cases of variola and in the blood of the variolated monkey. Bodies of like appearance may occasionally be found in the blood of vaccinated children and monkeys. A nucleus has not been positively made out in any of these bodies.

The above statements, which form the essential part of the conclusions with which Reed closes his investigation, show that he divides his findings into two classes, one of which, those of the first order, being occasionally found in normal blood, and those of the second order having been found only in cases of variola, variolated monkeys and occasionally in vaccinated children and monkeys. The appearance of these different forms is accurately described in his Experiments 11 and 12, as follows:

Experiment XI.—Monkey. Vaccination June 6, 1896. Successful. This animal's blood had been examined daily by two observers from May 22d to June 5th with negative results. There are seen, however, prior to vaccination, from time to time small, roundish bodies having a slightly greenish refraction and no distinctly granular protoplasm. These are in diameter about one-third that of a red cell and possess amœboid movements. Small, short processes are projected which quickly assume the same greenish color as that of the body proper. They are not to be confounded with the granular bodies seen in vaccinia. After vaccination daily examinations are negative till June 12th (sixth day). On this day the granular amœboid bodies appear in the blood in moderate numbers. They are in all respects similar to those described in Experiment V, except that some of them are smaller, having scarcely a diameter of one-sixth that of a red cell, and some have a slightly coarser and darker granulation. Distinct, clear, blunt processes are projected by these bodies into which, as a rule, the granular protoplasm does not flow, though exceptionally this is seen to take place.

*Walter D. Reed, M. D., On the appearance of certain amœboid bodies in the blood of vaccinated monkeys (Rhœsus) and children and in the blood from cases of variola. *Journal of Experimental Medicine,* Vol. II, p. 515.

Several of these granular bodies are still amœboid at the expiration of thirty hours. On the 12th day a body unlike any heretofore seen in monkey's blood is found. Its diameter measures one-half that of a red cell, and the body consists of a number of dark granules situated in the midst of a clear protoplasm. This body is rapidly amœboid, its clear periphery continually changing form and sometimes assuming rosette shapes (Plate XL, Figs. 1-9). A few granular bodies are present on the 14th day. Examination on the 15th, 16th and 17th days negative. (Fig. 1-a.)

Experiment XII.—Child, 4 years, white. Vaccination June 23, 1896. Successful. Examination of the blood on the day preceding vaccination is negative. Examination of blood taken thirty minutes after vaccination shows one small, faintly granular body, in diameter one-third that of a red cell, which sends off clear, blunt processes after the manner of the bodies already described in the vaccinated monkey's blood. From this time until the 7th day examinations are negative. On this day there are observed a few pale amœboid bodies, with a diameter one-half that of a red blood cell, containing a few fine, dark, dancing granules and which are slowly amœboid. Similar bodies are observed on the 9th day. Examination on 10th, 11th and 12th days is negative. (Fig. 1-b.)

From this description and the drawings illustrating Experiments 11 and 12 the similarity of the bodies described by us and those found by Reed is apparent.

In Vol. 164, Part 2, of Virchow's Archiv, in an article entitled "Untersuchungen über die Blutplättchen," Deetjen reports the results of a new method for the investigation of the blood platelet. This observer has succeeded by special means in showing that the blood platelets normally found in the blood under certain conditions (placing the fresh blood upon agar films, to every 100 c.c. of which has been added 6 to 8 c.c. of a 10 per cent solution of $NaPO_3$ and 5 c.c. of a 10 per cent solution of K_2HPO_4) increase in size up to forms as large or somewhat larger than a red blood cell and take on active amœboid movement. After fixation with osmic acid vapor and staining with hæmatoxylin, the central portions of these bodies stain more deeply than the periphery. The deeply staining portion at the center is interpreted by Deetjen as a nucleus, and he concludes that the blood plates are therefore definite elements which, under certain conditions, are capable of taking on an amœboid phase.

After first describing the usual degeneration phenomena which blood platelets undergo in blood after withdrawal from the body, he describes the behavior of these elements when placed upon agar

films impregnated with the salts above mentioned. In the course of five minutes, in most cases somewhat sooner, or in others later, the blood platelets are found to undergo certain changes. The platelets are first seen in the usual form of round or oval plates and are usually present in considerable numbers. In this stage they are apparently in a state of rest comparable to the spherical form taken on by the leucocyte in the stage of contraction. From this form they gradually become larger and two different substances can be detected within them; a central, highly refractive portion, usually round and of greenish color and an outer, paler protoplasm. The outer protoplasm immediately sends out pseudopodia. These are projected with great rapidity from various portions of the periphery and are either blunt or pointed. In this way the outline of the blood platelet is continually changing. Fig. 2 represents an attempt to indicate the changes in form which a single blood platelet undergoes in less than half a minute. In this case, of course, no attempt has been made to actually draw the changes of form, for when the composition of the agar is most favorable, these changes are altogether too rapid. Frequently the blood platelets are found, during the period in which they are actually projecting pseudopodia, to move slowly about the field. This is without doubt an independent amœboid movement. The smallest forms as well as the largest possess this power to move themselves about.

From the description above given it will be seen that the blood platelets, although closely conforming to the small, granular amœboid bodies of Reed, differ from the second order described by him in the absence of pigment. It is difficult to say as to whether the highly refractive central body which Deetjen holds to be a nucleus and the statement which Reed makes that he has never demonstrated a nucleus, are simply differences of interpretation or represent actual differences in the amœboid bodies in question. In the larger bodies which we have observed in the peritoneal fluid in cases of cancer we have observed a certain condensation of the central portion of the protoplasm which we held to represent a nucleus; but a nucleus, in the sense of nuclei, as we know them in tissue elements, has, of course, never been observed.

After a comparison of our own observations with those of Reed and the more recent results of the investigation of Deetjen one would be inclined to dismiss the entire matter with the belief that both Reed and ourselves had simply observed the amœboid form of the blood platelet. This would be the case, had we not recently become acquainted with the amœboid form of the parasite Plasmodiophora Brassicæ. The swarm spores of this organism are minute masses of protoplasm which, when first liberated from the spore cysts (see Figs. 1 and 2) are homogeneous. They are from 3 to 4 micromillimeters in diameter, but increase in size until they become transformed to typical myxamœbæ.

In the swarming stage these organisms frequently show active amœboid motion, rapidly throwing out and retracting pseudopodia and spine-like projections from the margin of their protoplasm. They frequently contain one or more granules of pigment and a nucleus is not demonstrable. A comparison of the illustrations from Woronin (Fig. 3, Article on Plasmodiophora Brassicæ) will at once show the similarity of this phase of Plasmodiophora to the amœboid bodies in question. The difficulty of fixing and staining this form of Plasmodiophora as well as the lack of success in fixing and staining the amœboid bodies in vaccine and those which we have seen in the peritoneal fluid in cases of cancer, have thus far frustrated any attempt at a more accurate comparison, and until more suitable methods are developed, the entire matter must be left in abeyance. While the work of Deetjen suggests a more simple solution of the significance of these bodies, certain forms of organisms belonging in the class of Plasmodiophora Brassicæ so closely resemble them that it is not impossible that they represent the amœboid form of some parasite. The lack of well-defined characteristics in the swarming stage of the Myxomycetes greatly increases the difficulty of the problem, but the recognition of the fact that such forms do exist cannot fail to advance our knowledge and may possibly lead to an explanation of some of the obscure problems in infections of undetermined etiology.

Since our last publication we have found but one case of peritoneal fluid in cancer in which we detected the actively moving amœboid

PLATE I.

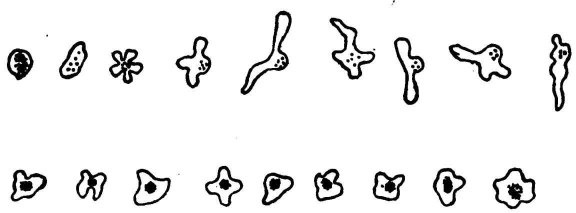

Fig. 1, after Reed.

Fig. 2, after Deetjen.

PLATE II.

Fig. 3. Inoculation carcinoma of dog's liver; *a*. periportal area; *b*. normal liver; *c*. nodule.

Plate III.

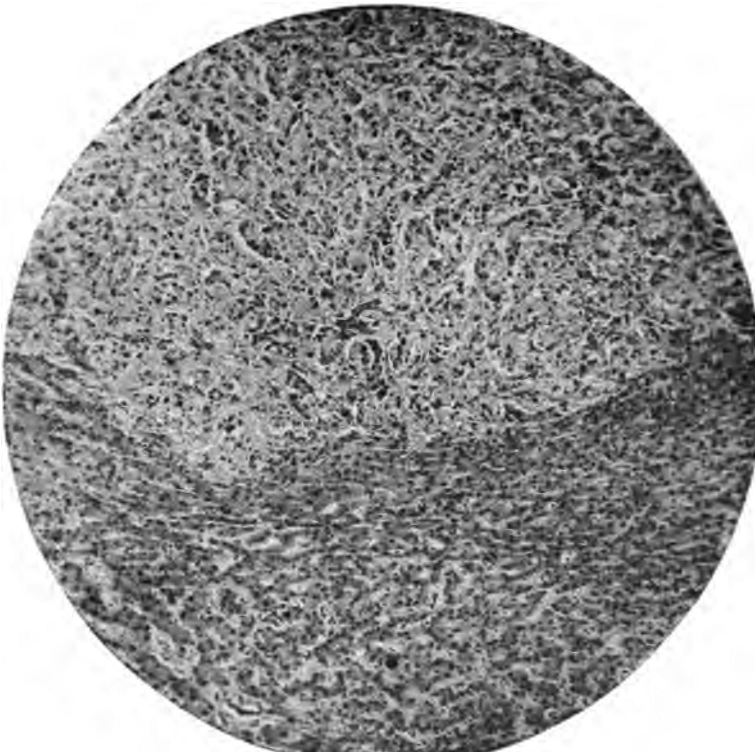

Fig. 4. Margin of inoculation carcinoma in dog's liver. Low power.

Plate IV.

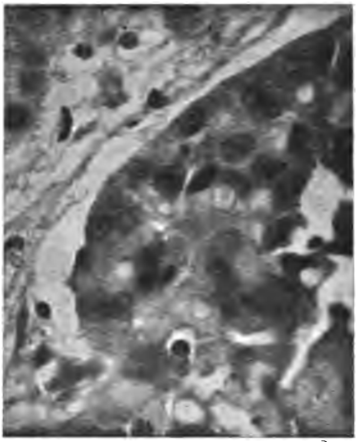

Fig. 5.

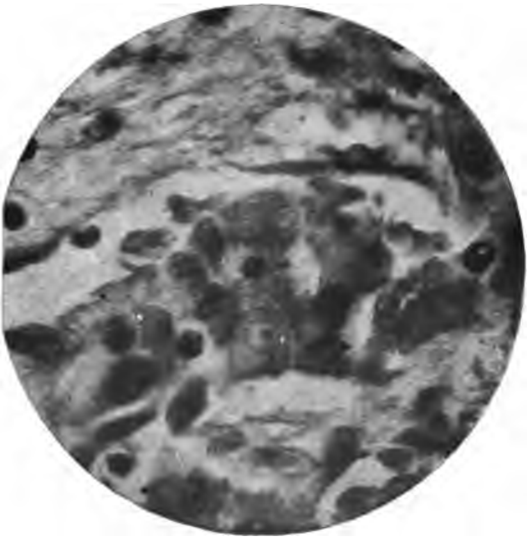

Fig. 6.

Fig. 7.

Fig. 8.

forms already described. A number of animals were injected with this fluid, and in one of them, a dog (No. 18), which we arbitrarily killed some ninety days after injection, we found that the liver was filled with firm, whitish nodules which, on section, proved to be new formations derived from the hepatic epithelium. The tissue was hardened in sublimate and on sectioning and staining, according to Plimmer's method, a lesion of almost unique characteristics was found. The nodules varied in size from that of a grain of rice to that of a small pea. They were essentially all of the same character and a description of one will suffice for all.

Under low power the nodules may be readily distinguished by the fact that the epithelium of the nodule is not as deeply stained as that of the surrounding hepatic parenchyma. At the margins of the nodules areas will be found in which the hepatic parenchyma is flattened, but at the greater portion of the periphery the cells are seen to lose their typical arrangement, grow irregularly into the structure of the nodules, staining more brilliantly with the neutral red and present a great variety of form. (Fig. 3.) This merging of the typical arrangement of the hepatic epithelium into the irregularly formed epithelium of the nodule is quite abrupt. (Fig. 4.) With low power numbers of vesicular inclusions can be seen in the epithelium of the nodule. These are extremely frequent, nearly every cell containing one or more. Toward the center of the nodule these inclusions are apparently larger than those near the periphery. At three different points in the periphery of the nodule, are included perivascular connective tissue areas. In each of these the connective tissue stroma is but slightly affected, with the exception of a moderate amount of round-celled infiltration. The epithelium on all sides shows definite evidence of proliferation, whereas the stroma of the periportal area and the epithelium of the gall ducts is unchanged. At the margin of one of these periportal areas is a narrow strip of hepatic epithelium, which has, for the most part, retained its distinguishing characteristics.

Under high power the cell inclusions can be readily distinguished and present all the characteristics of the so-called bird's eye inclusions. (See Figs. 5, 6, 7, 8.) They vary in size from 3 to 10 micro-

millimeters: The smaller bodies are distributed about the periphery of the nodule and a careful examination of the adjoining normal hepatic structure shows that *without exception the inclusions stop abruptly at the margins of the nodule. In no case have we found a single inclusion beyond the area of transformed epithelium.* The epithelium forming the nodule presents many bizarre forms, the nuclei stain deeply, the outlines of the cell are irregular, the protoplasm takes the neutral red. Passing toward the center of the nodule it will be found that the majority of the inclusions increase in size, and in some cases the structure shows evident signs of disintegration. In many cases the protoplasm of the cell is distended by a large vacuolar space, and in some of these spaces well-preserved leucocytes can be found. It would appear that at the center of the nodule the inclusions have undergone disintegration. Careful examination of the inclusions shows that the predominating form is that with a well-defined margin and spherical or irregular central body. In some of the inclusions the central portion of the central body takes the nuclear stain. In some of the larger inclusions a central body, with grains of chromatin distributed in a circle midway between the center and periphery, are to be found. These larger inclusions frequently present the appearance of poorly formed cysts embedded in the protoplasm, and in some groups of hyaline bodies are easily distinguishable. This transformation in the inclusions suggests some abortive attempt at development. The penetration of leucocytes into the larger structures is in our experience unique. We would conclude from the appearance of the epithelium of this nodule that we are dealing with an infection of the hepatic epithelium progressing at the periphery. A few karyokinetic figures can be found, and the evidences of compression, at certain portions of the periphery of the nodule, indicate that it is increasing in bulk. *The appearance of the epithelium and the entire structure of the nodule are those found in primary carcinoma of the liver.* The arrangement and distribution of the inclusions indicate that they are intimately associated with the proliferation of the hepatic epithelium.

In the light of this experiment we are naturally inclined to adhere to our belief in the specific nature of the small amœboid bodies which

we have observed in the peritoneal fluid. We have examined a number of peritoneal exudates in cases of widespread carcinoma of the abdominal organs without finding them. It is therefore evident that they are not always present. We have been unable to determine the conditions under which they appear, and it is not improbable that they are present at certain times during the progress of the disease and absent at others. The lesions which we have thus far observed in animals, as the result of inoculation or injection with peritoneal fluid containing these amœboid bodies, have led in a few instances to epithelial proliferation, in this *last case associated with the presence of large numbers of intracellular inclusions presenting all the characteristics of the typical bird's-eye inclusions in cancer.* At the same time these proliferations have presented the characteristics of primary infections of the epithelium and in no case have been associated with metastasis. We are, therefore, inclined to the belief that they are abortive and represent an unusual state of affairs produced by the unnatural introduction of the organism under such conditions that it is incapable of producing more than a temporary proliferation of the epithelium. While this line of investigation has proven extremely suggestive, it does not seem to us that in this way the problem can be brought to ultimate solution. *It is extremely probable that the introduction of an ectogenous cycle, probably in the body of some intermediate host, is necessary before the organism is capable of a primary infection.*

For the purpose of increasing our knowledge of parasites, which might be viewed as being more or less distinctly related to the forms we have observed in cancer, which we believe to be parasitic, we have undertaken an investigation of certain protozoan parasites, and because of striking characteristics which the organism presents we have undertaken a study of the intracellular parasite of clubroot, known as Plasmodiophora Brassicæ. A description of this organism, so far as our investigations have led us, is hereby submitted.

PLASMODIOPHORA BRASSICAE (WORONIN).

By Harvey R. Gaylord, M. D.

This organism, discovered by Woronin in 1876, is the recognized cause of a disease of many of the edible Cruciferæ, notably all kinds of cabbage, cauliflower, turnip, radish, kohlrabi, and, according to Tubeuf, has also been found in *Iberis umbellata, Capsella bursa-pastoris, Mathiola incana.* The infection of the vegetables above named by this organism is followed by the development upon the roots of tumor-like outgrowths and swellings of varying size and bizarre form. (Fig. 1.) The foliage of the infected plant is usually stunted, and as the disease progresses shows such evident wilting that the infected plants can be readily detected by this means alone. The disease has a very extensive distribution and is of considerable economical importance. It is known in this country as "clubroot," "clumproot" and "clubbing." In England it is usually spoken of as "finger-and-toe disease" or "anbury"; in Russia, where the organism was discovered, "kapoustnaja kila"; in Germany as "kohlhernie," "kohlkropf" or "vingerzichte," and in Belgium and France as "maladie digitoire." The distribution of the parasite seems to be as extensive as that of the plants which it infects. The disease produced such ravages in Russia that in 1872 the Royal Association of Gardeners offered a prize for the discovery of the cause and a means of prevention. The disease was first noted in Scotland in 1789. According to Eycleshymer, writing in 1891, the stronghold of the disease in the United States is in New England and the Middle States, especially in Connecticut, Rhode Island, Massachusetts, New Jersey and Delaware and the southeastern portions of New York and Pennsylvania. It had at that time, however, extended to Maryland and Virginia and the Carolinas. It had also been noted in Missouri, Wisconsin, Iowa and Michigan. This author has also called attention to the fact that the disease occa-

sionally develops in newly broken ground where no crop has yet been grown, and believes that this indicates that certain soils harbor the organism as a saprophyte. The disease is most prevalent in unusually wet seasons, and is almost endemic on land which is poorly drained and damp. It seldom occurs where the loam is sandy or calcareous. The same author calls attention to the fact that in the neighborhood of limestone outcroppings the vegetables are comparatively free from attack, and states that on Long Island the gardeners raise their cabbages year after year on the old shell heaps without any trace of the disease. The disease is known to occur in fields which have been covered with compost, where the adjoining fields which had not been fertilized were free from attack.

The organism which produces these outgrowths and tumor formations presents many points of interest. Woronin, who gave it the name of Plasmodiophora Brassicæ, classified it among the Myxomycetes, an order of uncertain position, but generally viewed as lying midway between the animal and plant kingdoms.

DeBary,[1] who considers this order to belong more properly to the animal than to the plant kingdom, has suggested the name *Mycetozoa,* which, according to more recent classifications, is preferable. Certain groups of these organisms present characteristics which identify them with the lowest forms of plants, while others present characteristics which unmistakably indicate that they are of protozoan nature. To this last group undoubtedly belongs *Plasmodiophora Brassicæ.* Doflein[2] so classifies the organism, and in fact places the order *Mycetozoa* under the *Rhizopoda.* The lower forms of this order present many points of similarity to the *Amœbæ* and the *Heliozoa,* but differ distinctly from these organisms in their developmental cycle. In fact, very little is known about the entire class, and without doubt many points in the cycle still remain to be determined. Duflein divides the order into two suborders, Protomyxidea and Mycetozoidea.

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[1] Comparative Morphology and Biology of the Fungi, Mycetozoa and Bacteria. 1887.

[2] Die Protozoen als Parasiten und Krankheitserreger nach biologischen Gesicthspunkten dargastellt. Jena. 1901.

The organism we are considering is placed by this author in the first suborder. The developmental cycle of these organisms differs according to their position in the scale. The higher, those which most closely approximate the fungi, present more or less complicated cycles, but in none has a sexual phase been determined. So little is known about them, however, that it is highly probable that we are but imperfectly acquainted with the life cycle of even the lowest forms. The simplest form of the Mycetozoa is found in a minute mass of protoplasm, the so-called swarm spore, which develops into Myxamœbæ. In this phase the Myxamœbæ may change their form, protrude delicate flagella and are then known as myxoflagellates. The flagellate and amœboid forms are practically interchangeable. As an amœba the organism contains a more or less well-defined nucleus and occasionally a contractile vacuole. It may divide and in this way increase in number; it may become encysted as a single amœba, or certain of the organisms may increase in size until cysts of considerable dimensions are formed in which there develop a number of spores. In all probability this stage is preceded by some form of copulation as yet undetermined. The spores in this case, after liberation from the cyst, probably develop within them swarmers, which, on escaping, take on the form of myxamœbæ or flagellates. Fig. 2, adapted from Doflein, illustrates what is known of the cycle of the *Protomyxidea,* the suborder to which *Plasmodiophora* belongs. Question marks inserted in this cycle indicate that possible intermediary stages are as yet undetermined.

The organism *Plasmodiophora* as described by Woronin was first noted in the spore form as minute, spherical, yellowish-green bodies of uniform size, filling the enlarged cells of the infected plant. (Fig. 3.) These cells were usually arranged in groups. Besides the spores, Woronin recognized the presence in certain cells of large masses of protoplasm more or less filling out the sap spaces of the cell. These he viewed as the plasmodial form of the organism.

As to the ectogenous phase of the parasite, Woronin noted that the spores presented a definite delimiting capsule within which granular protoplasm could be detected. The mass of protoplasm within the cyst later developed into a definite body or swarmer which, on the

PLATE V.

Fig 1.

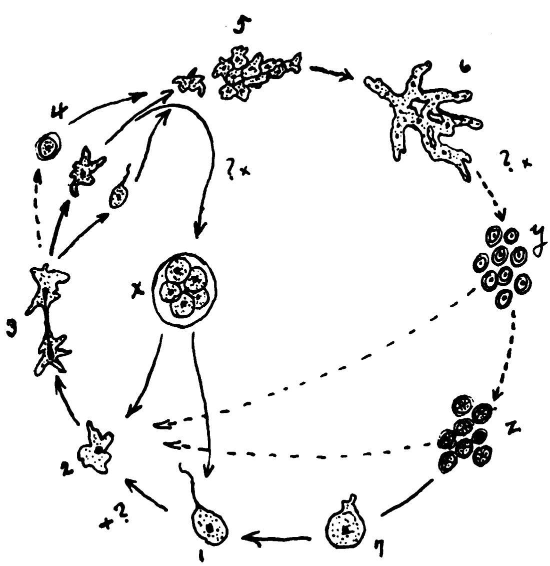
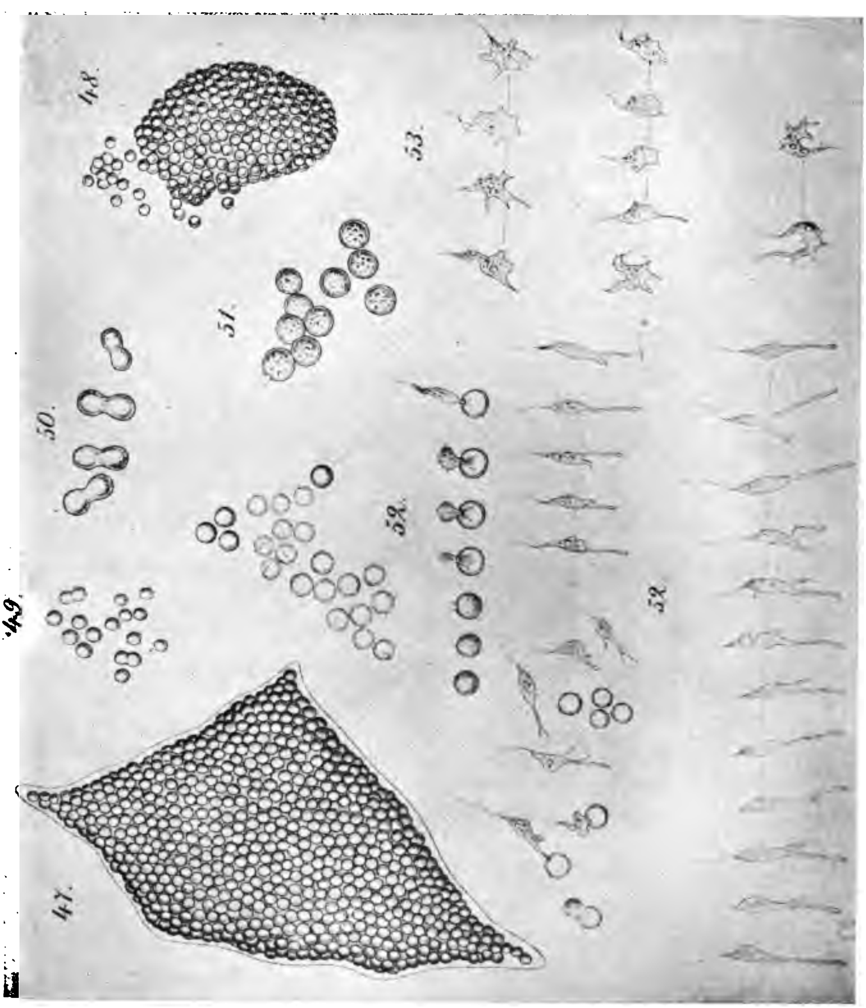


Fig. 2.

PLATE VI.

Fig. 3.



Figs. 47, 48, 49, 50, resting spores; 51, beginning germination; 52, escape of the myxamœbæ from the cysts; 53, free amœbæ.

bursting of the cyst, was liberated and thereupon took on the form of an amœba, showing more or less active amœboid motion, or protruding delicate flagella and moving about the field in the form of a flagellate. Fig. 3, after Woronin, sufficiently illustrates this phase of the organism. Woronin determined that the organism observed was the cause of the tumor-like outgrowths in which they were found, by infecting ground with the dried roots of infected plants. By so doing he established beyond question the relation of the organisms to the disease.

Upon the disintegration of the roots the spores of the organism remain in the ground until the following season, when with the advent of warm weather the swarm spores are liberated from the spore cysts and infect the growing plants. The exact method by which the amœboid or flagellate form of the organism enters the uninfected plant has never been definitely determined, but it is generally supposed to be by means of the root hairs.

Infection may occur, according to Woronin, at any period during the life of the plant and affects not only early but late vegetables.

The article of Woronin remained for many years the only extensive investigation of this organism. Many notes as to its occurrence, methods of prevention, etc., are to be found in the agricultural literature, but no advance was made in the subject until the publication of Nawaschin.[1] This author undertook an investigation with modern histological methods to clear up the obscure phases of the organism in the plant cells, to investigate the changes produced in the plant by the organism, and the nature of the relations between the cell and the parasite. It may be remarked that the closing paragraph of Woronin's article called attention to a possible relation between these tumors in plants and those found in man and animals. The wording of this paragraph is so significant in the light of present investigation and it is so seldom referred to, although made in 1878, that it would seem desirable to give it verbatim:

Ich vermuthe nämlich, dass die Erscheinung und Entwickelung vieler pathologischer Auswüchse und Anschwellungen, die auf dem thierischen Organismus vorkommen, auf folgende Weise erklärt werden können: In

[1] Flora. Bd. 86, H. 5, 1899.

den lebendigen Organismus dringen, auf irgend welchem Wege, kleine Myxamöben ein, die sich allmählich in Plasmodien entwickeln und im Gewebe dieses oder jenes Organs eine bedeutende Reizung hervorrufen; dieses verursacht im Organ eine pathologische Veränderung des ganzen Gewebes, von welcher denn auch die Form und Grösse der krankhaften Auswüchse oder Anschwellungen abhängig sind. Nächstfolgende Untersuchungen werden zeigen, ob meine Vermuthung sich bestätigen lässt.

In the introduction to this article Nawaschin calls attention to the closing paragraph of Woronin's article above given and notes the fact that from the standpoint of general pathology Plasmodiophora is worthy of special attention as an intracellular parasite, producing a specific tumor which bears many analogies to the so-called "malignant" tumors in animals and man. He furthermore calls attention to the fact that Plasmodiophora undoubtedly stands very close to the Sporozoa, the recognized cause of many infections in animals. Nawaschin's work deals exclusively with the results of sectioning and the staining of the plant tumors and has thrown much light on the intracellular phases of the organism. This, he finds, makes its first appearance within the plant cell in the form of a well-developed amœba, which in osmic acid preparations (Flemming or Hermann) may be immediately detected within the plant cell as a mass of closely packed, regular, blackened, granules. On careful examination with higher powers these granules are found to be embedded in a mass of protoplasm with more or less well-defined outlines. (Fig. 4.) Between the granules one or more clear spaces will be found within which a spherical, centrally placed body, bright red in safranin preparations, can be distinguished. These prove, on further observation to represent nuclei. If the osmic acid is removed from the preparations these nuclei are found to be surrounded by the protoplasm of the amœbæ. The youngest amœbæ observed by Nawaschin have always possessed at least two nuclei. These present definite characteristics. They are spherical or oval in the resting stage, have a fairly well-developed nuclear membrane, are apparently filled with a clear fluid and possess a highly refractile central body, as he expresses it, "of nucleolar nature." The infected plant cells are always arranged in groups, and each cell usually contains more than one amœba.

PLATE VII.

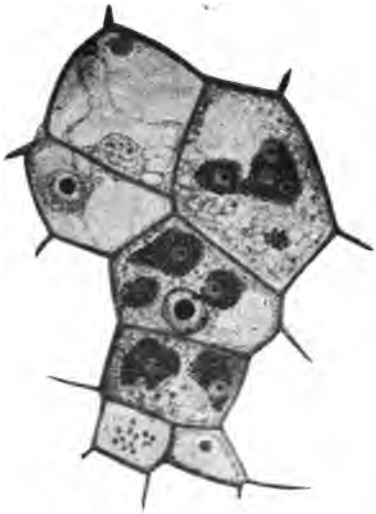


Fig. 4.

Fig. 5.

Fig. 6.

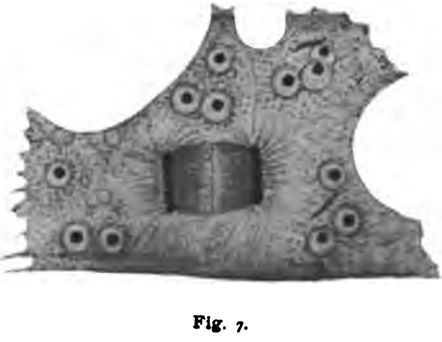


Fig. 7.

The normal plant cell possesses a well-defined membrane of cellulose lined by a narrow layer of protoplasm which extends in bridges to the nucleus, which lies in varying positions within the cell cavity. The spaces between the bridges of protoplasm are filled with cell sap. It is within the sap spaces that the amœbæ first make their appearance. The method of their entry as swarm spores into the infected plant is, as we have stated, as yet undetermined. The nucleus of the plant cell is spherical, oval or of irregular shape, possesses a nuclear membrane and a large, spherical or irregularly shaped nucleolus. It is many times larger than the diameter of the largest nuclei in the amœbæ and can readily be distinguished by its characteristic appearance. The conditions within the plant cell are so simple that the morphology of the parasite and its relation to the cell can be determined with great accuracy. Fig. 4, after Nawaschin, represents a preparation from which the osmic acid has not been removed and the amœbæ are seen within the plant cell sharply defined by the regular, black granules embedded in their protoplasm. The differentiation of the protoplasm of the amœbæ in preparations from which the osmic acid has been removed is not invariably well-defined. This is especially true of the very young organisms. In these the protoplasm of the organism may be poorly developed, and in fact consist of mere threads extending into the surrounding plant protoplasm, in which it is apparently lost. Figs. 5 and 6, from Nawaschin, represent two young amœbæ immediately after division of the nuclei. The protoplasm in these cases presents the characteristics just mentioned.

While Woronin believed that the increase in number of amœbæ within certain cells was probably owing to the fact that the organism at this stage passed from one cell to the other, Nawaschin has shown that this interpretation is incorrect. He has never been able to detect any amœba in the act of passing through the wall pits of the cells. He has been able to determine that they increase in number by division, that the presence of the organisms for a long period causes no change in the plant cell; that during this stage *the organism lives in a state of symbiotic relation with the host cell, until through proliferation the number of amœbæ in the plant cell makes sufficient*

demands upon the nutrition of the cell, whereupon the host cell divides by the regular process of karyokinesis. The amœbæ in this case are more or less equally distributed in the daughter cells. (See Fig. 7, from Nawaschin.) By this means, according to Nawaschin, the organism is distributed in the diseased portions of the plant. The fact that the infected cells lie in groups is thus explained. When, however, the demand upon the infected cell can no longer be met and the nutrition is finally exhausted, the amœbæ pass through certain preparative changes, finally coalesce to plasmodia, the nuclei all divide by the regular process of karyokinesis and the entire mass is divided up into minute myxamœbæ, each with a single nucleus. These myxamœbæ secrete a membrane about them, take on a spherical form and become condensed into spherical spores. There is no sac (peridium) formed about the plasmodium in this process of spore formation, but as Woronin has pointed out, in all probability the absence of the peridium is due to the fact that there is no necessity for this formation, the walls of the exhausted plant cell performing this function.

The first evidence of nuclear division is found in the appearance within the clear space between the periphery and central body of minute grains of chromatin irregularly placed. These arrange themselves in a plane, which later becomes that of division, in a circle about the central body. This first becomes elongated and then divides. A longitudinal section at this stage shows two closely approximated central bodies with two small grains of chromatin in the plane of division, but close to the divided central body. In cross section this figure usually presents the appearance of a rosette, the central body being surrounded by more or less equi-distant granules of chromatin. The central bodies then withdraw to the poles of the cell and half of the chromatin becomes intimately associated with each. The elongated nucleus is then divided into two spherical smaller nuclei by the capsule passing into the center and coalescing. In this phase it commonly occurs that the entire elongated nucleus is bent upon itself, which results in the nuclei, when completed, being placed at a slight angle to each other and presenting a characteristic appearance, as shown in Fig. 6, from Nawaschin. Nawaschin has

not attempted to analyze this method of nuclear division, but it will be seen that it is entirely distinct from the process of coalescence and regular karyokinetic changes in the resulting plasmodium which terminates in spore formation.

It will be seen by observing the illustrations taken from Nawaschin that the nucleus of the amœboid form of Plasmodiophora presents a very distinct similarity of appearance with the cell inclusions noted in cancer, a fact which has been noted by von Leyden and others.

The analogy between the tumors resulting from the infection of the plant by this organism and malignant tumors in man and animals, as pointed out by Woronin, was emphasized by the observations of Behla,[1] who noted the great frequence of clubroot in the gardens of the inhabitants of a certain portion of the town of Luckau, in which cancer was particularly prevalent. He likewise found that fragments of the plant tumors inoculated into animals produced swellings and tumor-like formations, but he was unable to detect the parasite in the animal tissues. A more direct support of the analogy is to be found in the preliminary statement of Podwyssotzki, 1900, who found that animals inoculated with fragments of clubroot developed tumors which possessed certain points of similarity to the sarcomata and endotheliomata. The attention of Podwyssotzki was attracted to Plasmodiophora Brassicæ through the work of Nawaschin, both of these observers being members of the faculty of the University of Kieff. Podwyssotzki's conclusions are of such great interest that it is desirable to quote them in full:

1. It is possible to produce by inoculation with Plasmodiophora Brassicæ tumors in animals, thus far rabbits and guinea-pigs.

2. These tumors are of mesodermic origin and in the progressive stage are similar to large celled sarcomata or endotheliomata, or the granulomata found in leprosy.

3. These tumors are the result of a marked hypertrophy and proliferation of the fixed connective tissue elements, especially the endothelium of the perivascular lymph spaces. One is, therefore, justified in speaking of a mycetozoan perithelioma or granuloma. The proliferation leads to the formation in the neighborhood of the blood vessels of larger or smaller infiltrations or nodular formations. Leucocytic infiltration is demonstrable

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[1] Behla. Die geographisch-statistische Methode als Hülfsfactor der Krebsforschung. *Zeit. f. Hygiene u. Infectionskrankheiten*, Vol. 32, p. 123.

in the first stages of the infection, but disappears from the eighth to the twelfth day.

4. The spores of Plasmodiophora Brassicæ are found in the tumor cells either singly or in great numbers. In the latter case the cells are greatly distended and the spores are surrounded by a mucin-like substance which gives the whole the appearance of a plasmodial mass filling the body of the cell.

5. The more mature tumor cells contain the greater number of spores. Many of these are so greatly distended and show such marked vacuolization that they are apparently being destroyed. For this reason the central portion of the tumor is often represented by a yellowish, half dry mass of disintegrated cells.

6. The most peripheral or youngest elements of the tumor contain fewer of the spores. These are difficult to demonstrate. It can only be accomplished by a careful comparison of the different stages of metamorphosis from the centrally arranged older cells of the tumor containing large numbers of well-defined spores.

7. In many places in these tumors may be found giant cells, including within their bodies numbers of spores. In some of these giant cells the spores have disappeared.

8. The nuclei of the infected cells for a considerable period show no changes aside from increase in size and chromatin content. Many of the cells containing spores show evident mitosis, proving that the parasite induces proliferation of the nuclei.

9. The picture presented in these nodular formations can be most easily understood as evidence of specific phagocytosis, as undoubtedly many of the spores are destroyed within the cells, in which case they gradually become incorporated with the protoplasm of the cell and can no longer be differentiated. It was undoubtedly the cells of this sort which were observed by Behla and which led him to the conclusion that portions of clubroot after transplantation into animals produced infection, although the parasites could not be detected within the cells.

10. It would seem that the nuclear substance of the spore undergoes a progressive metamorphosis. In many of the spores two or more chromatin containing nucleoli may be found. The spore in this case presents an appearance suggestive to the differentiation found in mitosis. It is, however, impossible to affirm with certainty that an actual increase of elements within the spore occurs. This question must be the subject of future investigation. In many cells, however, the parasite may be found without the characteristic capsule. Under any circumstances it would be difficult to explain the infection of cells so far from the center of the tumor without an increase of elements within the spore, as it is impossible that the comparatively large spores (about the size of an erythrocyte) should be carried by the lymph through the small lymph spaces. Spores within the leucocytes have never been encountered.

11. The larger cells in sections fixed in Flemming's fluid present an extremely interesting picture. Surrounding the single spores the adjacent protoplasm of the tumor cell is filled with closely arranged minute fat droplets, so that the infected cell is readily detected even with low power. Such cells present the appearance of a vacuolated cell, each vacuole surrounded by fat droplets. Under oil immersion the structure of the cell can be

readily determined, and it would appear that the minute fat droplets are a portion of the parasite, the protoplasm of which, in the vegetable tumors, is normally filled with fat droplets. The fat remains within the spores after implantation in the tissues of animals, so long as the spore remains free. It diminishes in the spores so soon as they are taken up by the connective tissue cells. When this has occurred the spores gradually lose their fat, with the exception of one or two minute fat droplets within the capsule.

12. In an extremely malignant case of sarcomatosis of the peritoneum, kidneys, thyroid and other organs of a child, from the clinic of Professor Tchernoff, I have observed the presence of cells presenting the characteristics of those above described. They were especially prominent in preparations hardened in Flemming's fluid, where they could readily be detected with low power because of the blackening resulting from the presence of the fat. Under oil immersion these cells were found to contain a number of minute round bodies within vacuoles. A further report of these parasitic inclusions will appear later.

Since the appearance of the preliminary statement of Podwyssotzki no one has apparently disproved or confirmed his results. One or two observers have confirmed the similarity of appearance between certain forms of Plasmodiophora and the inclusions in cancer (von Leyden, Feinberg) while others (Lubarsch, Nösske) believe that this analogy is not justified.

Results of inoculation experiments with Plasmodiophora.—Early in 1901, through the kindness of Professor Welch, we came into possession of the article of Nawaschin, which naturally fixed our attention upon the preliminary statement of Podwyssotzki, above mentioned. Since that time we have been experimenting with Plasmodiophora in various ways. Through the kindness of Dr. Erwin F. Smith, of the Laboratory of Plant Pathology,. Washington, D. C., we were placed in communication with Prof. L. R. Jones and Mr. W. J. Morse of the Agricultural Experiment Station at Burlington, Vermont. These gentlemen have repeatedly furnished us with young clubroots, grown for us in their greenhouses during the winter. Through Dr. Smith we were likewise placed in communication with Dr. M. C. Potter of the Durham College of Science, Newcastle-upon-Tyne, from whom we were able to obtain a quantity of clubroots from England. Careful comparison of the Plasmodiophora obtained from this source and that found in America shows no distinguishable difference. To all of the gentlemen mentioned

we are deeply indebted and desire to express our thanks for much assistance.

With the material obtained from these sources and with clubroot obtained from the neighborhood of Brookfield, N. Y., where the disease is prevalent, to which our attention was called by Dr. I. P. Lyon, and the neighboring town of Hamilton, where it is apparently still more prevalent, we have had no difficulty in infecting earth. Cabbages and other varieties of Brassicæ grown upon this ground, either in the greenhouse or in the open, in a prepared bed at the rear of our Laboratory, have supplied us continually with material. Fig. 8 is a photograph of a specimen raised in the bed above mentioned during the past summer. We began our investigations by careful examinations of the fresh material. The spores of the organism could be readily detected in freehand sections, or in scrapings from the fresh surface of the clubroot. Many of the infected cells were found filled with these closely packed spherical bodies. (See Fig. 3-43, from Woronin.) They measured 3.33 μ in diameter. Some of them were homogeneous (see Fig. 3-49, from Woronin). In some a delicate outline within the delimiting capsule could be observed, and in the majority one or more highly refractive bodies. *The relation of these spores to osmic acid was ascertained with the result that the various forms were found to blacken after treatment of a few hours. This blackening affected the capsule of the spore and the highly refractive central body. Where the spores were homogeneous they took on diffuse blackening.* The color was usually yellowish-green, rarely of a brownish tinge. *When treated with Sudan III, some of the spores stained intensely while others took up the stain less rapidly. In the spore forms containing a well-defined, highly refractive central body, this and the capsule were usually first blackened by osmic acid or stained by Sudan III, as the case might be.*

In young clubroots the amœbæ described by Nawaschin could be readily detected. These were found in the form of spherical or oval masses of protoplasm within the sap spaces of the plant cell, filled with coarse granules, approximately one micromillimeter in diameter. These granules were highly refractive and in many cases

PLATE VIII.

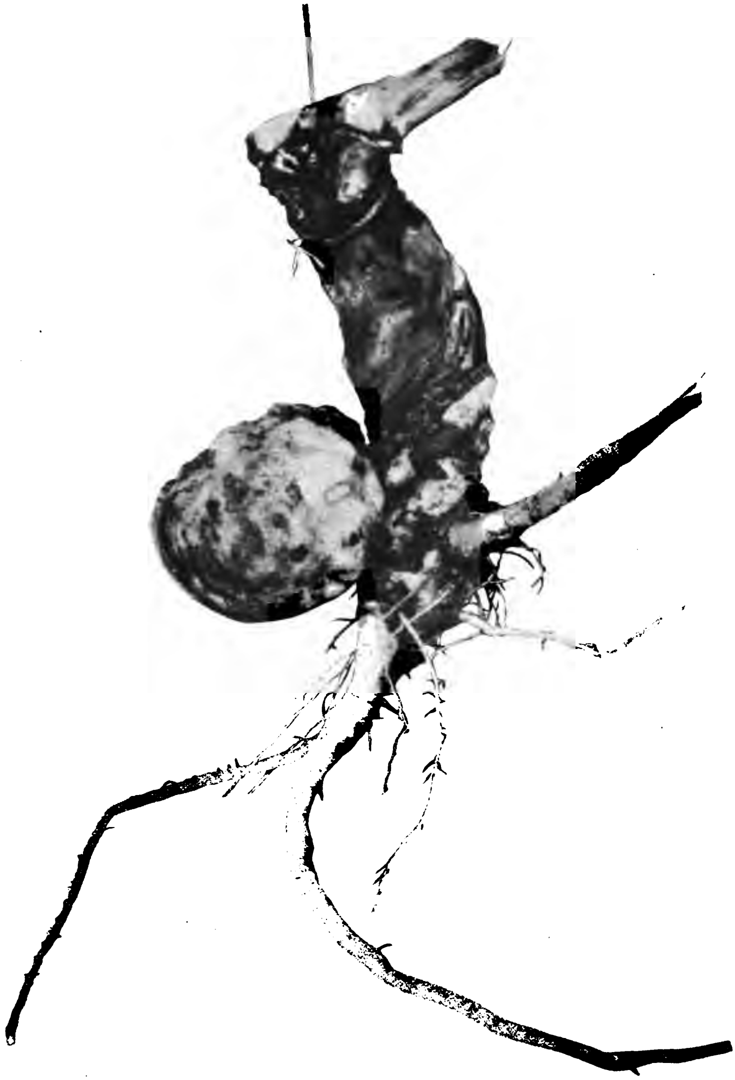

Fig. 8.

Club-root in the cabbage. Grown in artificially infected soil.

were in active motion. The nuclei of the amœbæ were visible as vacuoles in the protoplasm, and occasionally a highly refractive central body could be observed. The whole appearance of these forms, *with the exception of the nucleus,* could only be compared to that of an eosinophile, as they appear in fresh preparations. The striking character of this resemblance was extremely impressive. Occasionally free amœbæ could be detected in the fluid of the scrapings, in which case they were spherical, the granules usually in active motion. Attempts were made to fix and stain them but without great success, the best results being obtained in the sections to be described later.

This phase of the organism will continue to offer a field for research for some time. The observations thus far reported are largely confirmatory, with the exception of certain forms thus far undescribed. An article on the staining affinities of various forms of the organism will be published shortly by Dr. Matzinger, with whom the observations on the ectogenous cycle of Plasmodiophora Brassicæ were jointly conducted.

For the purpose of observing the development of the organism portions of dried clubroot were placed in flasks containing sterile water and allowed to remain at room temperature. In many cases the water in the flasks was rapidly overgrown by bacteria, but in a few cases where the bacteria did not develop with such rapidity we were able to trace the development of the swarmers within the spore cysts, their liberation from the spore cysts and their presence free in the fluid. The smallest recognizable form of the organism (swarmers) is a spherical, highly refractive body resembling a minute drop of fat, varying in size between 1 and 3 μ, *each having attached to it a delicate, thread-like flagellum, so fine as to be scarcely distinguishable even with the highest powers. This minute, spherical form of the organism moves about rapidly in the field by the movement of this delicate thread. In preparations treated with osmic acid the body of this form of the organism fails to blacken even after prolonged treatment.* The next recognizable forms of the organism are the myxamœbæ and myxoflagellates, the latter being more common. The swarmers can be seen developing within the spore cyst, as described by Woronin (see Figs. 3-51-52.) Our experience in this connection is of interest, inasmuch as no less an authority than

Tubeuf[1] has recently stated that he has never been able to observe this phase and that the late Professor Frank had likewise never succeeded in causing the spores to develop into cysts with the liberation of the swarmers. von Leyden has also made the same statement.

The development of the swarmers within the spores begins by the spore increasing in size to about 4 to 6 μ, the highly refractive body within the spore sac gradually disappearing and the contents of the sac taking on a well-defined granular character. This granular protoplasm (also shown by Woronin) gradually contracts until the mass within the spore sac can be easily distinguished from the surrounding membrane. At the proper time the spore sac bursts, liberating the mass of protoplasm, which, after passing into the surrounding medium, takes on the form of a myxamœba or of a myxoflagellate. The protoplasm of the organism at the time of liberation is homogeneous. A nucleus can occasionally be observed, but is extremely indistinct. All attempts to harden and stain the organisms in any of the forms described, have given but unsatisfactory results. In the most successful attempts the organism appears as a mass of protoplasm of rounded or irregular form, with a center staining somewhat more deeply than the surrounding protoplasm. We have never been able to demonstrate the presence of a contractile vacuole. The organism in this stage is so lacking in characteristics that all attempts to establish a means of identification have been unsuccessful.

Inasmuch as it is in this phase that the organism is supposed to infect the plant, we have attempted to detect the swarmers and flagellates in the tissues of animals. Cultures containing large numbers of the swarmers have been injected into animals intravenously and directly into the tissue, the animal being killed and the tissues hardened within a few minutes after the injection. In no case have we definitely succeeded in locating the swarmers by their appearance. *Once in the tissue, becoming rounded, they present an appearance so like structures usually interpreted as degeneration products, that it is impossible at present to recognize the organism with certainty.*

[1]Verhandlungen der Komité für Krebsforschung. Sitzung am 9 Januar 1902.

Examinations of clubroot by means of hardened and stained sections.—The staining method which we have principally utilized is the method of Plimmer, inasmuch as we desired from the beginning to compare the appearances of the organism to the cell inclusions in cancer, as demonstrated by this method. The method recommended by Nawaschin has likewise been employed, and as given by this author is as follows: Very small portions of the infected root are placed in strong Flemming's solution, where they are allowed to remain twenty to twenty-four hours, when they should be removed, as longer action of the fixative permanently blackens the protoplasm of the organism. After embedding in paraffin, sections two or three micromillimeters are cut and attached to the slide by cohesion. When it is desired to remove the osmic acid from the preparation the sections and slides are placed in hydrogen peroxide, full strength. Preparations are mounted in thickened cedar oil stained with Feinberg's safranin-gentian-violet-orange stain. Sections are first stained with one per cent safranin solution, washed in water and then counterstained with two per cent gentian-violet solution. Pass through alcohol and clear in clove oil which has been saturated with orange, in which they may remain a considerable length of time without overstaining. They may then be cleared with xylol and mounted in balsam, or cleared in commercial oil of cedar and mounted in thickened cedar oil.

This method gives excellent preparations, but in no way superior to those obtained by the method recommended by Plimmer for the demonstration of cellular inclusions in cancer.

Sections of mature clubroots are distinguished by groups of hypertrophic cells filled with closely packed spores. Preparations hardened in Hermann and stained with safranin show that many of the spores are blackened by the osmic acid. Those which do not show the black reaction stain diffusely with the safranin. The dense delimiting membrane in the unblackened spore can be detected by a slight difference in the refractive index. Within this an irregular outline, possibly representing the protoplasmic content of the spore, is distinctly visible. The spores present a most interesting appearance in preparations from which the osmic acid has been removed

and treated with the following steps of Plimmer's method. In this case it has been found that the reaction of the spore to the iron hæmatoxylin is almost as capricious as its relation to osmic. Many of the spores are stained a diffuse blue-black, in which case the internal structures are obscured. A certain number are entirely resistant to the nuclear stain, in which case the irregular internal structure can be readily observed. (Fig. 9.) The spores are of uniform size and measure, as above stated, 3.33 μ. The amœbæ present the characteristics already given by Nawaschin. In the younger roots examined they are the predominating form and *in the very young outgrowths the spores are entirely absent.* The nuclei of the amœbæ stain with a protoplasmic stain, Plimmer's method, thus presenting an appearance extremely like that of the so-called " Plimmer's body," the characteristic cell inclusion of cancer. They vary considerably in size in the different amœbæ, but the nuclei in each amœba are of practically the same dimension. (Fig. 10.) We have detected nuclei as small as two micromillimeters in diameter and others five micromillimeters. Most of the nuclei are spherical in outline, but many oval or fusiform nuclei will be encountered. The protoplasm of the amœbæ in osmic acid preparations is either granular or coarsely reticulated, depending upon the success of the fixation. The outlines of the mature amœbæ can be readily determined, *but in the younger forms, as pointed out by Nawaschin, the protoplasm is intimately associated with the protoplasm of the plant cell and is often poorly developed, in which case the nucleus presents an appearance extremely like the cell inclusions in cancer. The central body stains somewhat more intensely than the nuclear membrane. The nuclear membrane of the smaller nuclei is, as a rule, poorly developed, in many cases scarcely distinguishable, in which case the nucleus presents the appearance of a vacuole in the protoplasm containing a highly refractive central body.* Many of the cells are completely filled with closely packed amœbæ, in which case the cell protoplasm is practically obliterated. The infected cells lie in groups, as described by Nawaschin, but these groups are usually surrounded by hypertrophic plant cells containing no parasites. The nuclei of the plant cells are readily distinguishable from the amœbæ,

PLATE IX.

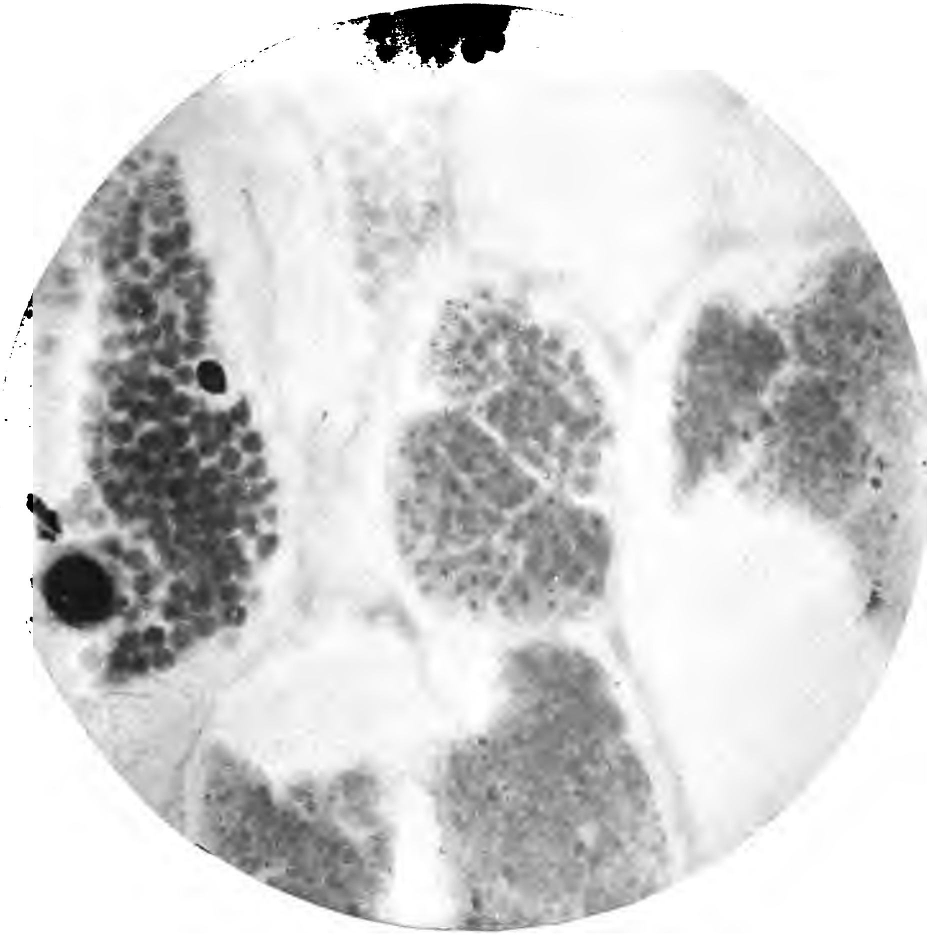

Fig. 9.

PLATE X.

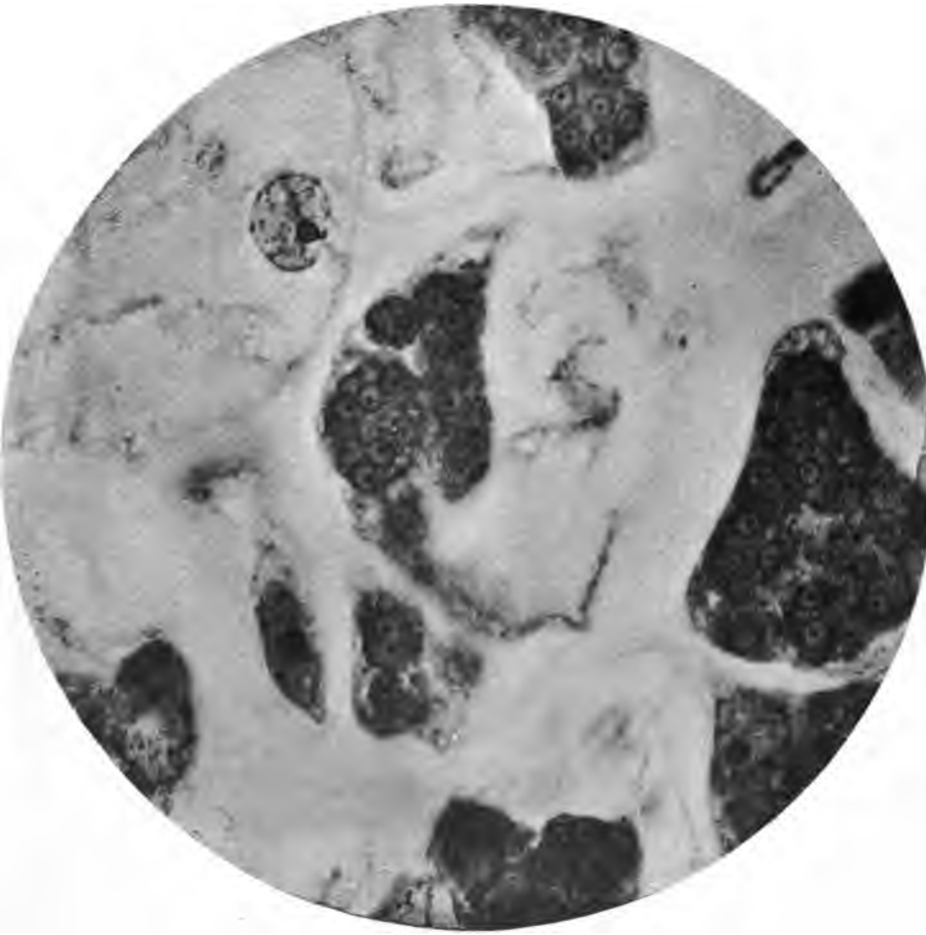

Fig. 10.

measuring on the average 10 to 12 micromillimeters in diameter. The amœbæ vary in size, the smaller measuring 4 or 5 micromillimeters, the larger 18 or 20 micromillimeters in their greatest diameter. The form of the amœbæ varies within wide limits, but the predominating form is oval or spherical. We have counted as many as 20 nuclei in one section of an amœba.

In the material thus far examined we have been unable to collect all the different forms described by Nawaschin, as evidence of nuclear division of the amœbæ, but divided central bodies with the grains of chromatin arranged in the plane of division are not infrequent. For this purpose young roots are required. The phases leading to spore formation are more readily discernible. Large amœbæ in which the nuclei are indistinct are extremely frequent. The outline of the amœbæ in this stage becomes indistinct (Fig. 9) and those adjacent to each other coalesce. Many of the cells are filled with granular masses of protoplasm nearly or completely filling the entire cell (plasmodia). (Fig. 9.) The nuclei of these masses of protoplasm, which are scarcely discernible, then divide by a process of regular karyokinesis, so that large masses are found filled with achromatic spindles, with well-defined medullary plates. At this stage the entire mass of protoplasm divides into irregularly shaped units surrounding the spindles, and these, according to Nawaschin, by a process of condensation form the spherical spores.

Infection of animals with Plasmodiophora.—Having determined the appearance of the spores, amœboid and plasmodial forms of the organism within the plant, both in the fresh state and in hardened sections, we have undertaken to repeat the experiments of Behla and Podwyssozki by implanting fragments of the tumor-like outgrowths of the infected roots beneath the subcutaneous tissue and into the peritoneal cavities of cold and warm-blooded animals. For this purpose we have employed guinea-pigs, rabbits, a few white rats and frogs.

The method of procedure was as follows: Fresh clubroot immediately after removal from the ground was washed for a period of time in running water, then carefully scrubbed with a brush to remove the dirt, after which it was thoroughly scrubbed in a 1:2000

sublimate solution, then thoroughly washed in sterile water. Observing the usual antiseptic precautions, sections of the tumor-like outgrowths 8 or 10 mm. in thickness were cut from the root, and with a sterile canula disks were punched from the cortical portion of the outgrowth, in each case avoiding the periphery. A slight incision was made through the skin in guinea-pigs and rabbits, the canula was introduced, the disk of clubroot pushed from the canula into the integument and the wound closed.

In all of the animals thus treated the wound healed rapidly without suppuration, except in a few cases where the clubroot was not sufficiently disinfected and bacteria were introduced. Where infection did not occur the results were uniform, whether the implantation was made in guinea-pigs or rabbits. In each case microscopic examination was made of the fresh material before implantation. Several animals were inoculated with very young outgrowths, the tissue of which, when examined with the microscope, showed only the presence of amœbæ within the plant cells, and in these cases *no infection resulted.* In the remaining experiments the microscopic examination showed the presence of many spores of the organism, which were likewise readily detected in the fragments of plant tissue remaining after removal from the animal at the termination of the experiment.

In all of these experiments there developed at the site of implantation a distinct tumor, which increased in size for a period of from four to six weeks, at which time they were usually the size of a hazelnut. From the sixth week on the tumors gradually decreased in size, and at the end of three months the site of the implantation was marked only by a small mass of connective tissue or had totally disappeared. The microscopic appearance of the fresh tumors during the stage of progression, i. e., to six weeks, was found on removal to consist of the remains of the implanted vegetable tissue surrounded by pinkish-white granulation tissue constituting the tumor. Scrapings from the cut surface of the tumor, avoiding the plant tissue, showed that the growth is composed of large cells of connective tissue or endothelial origin. These cells possess large vesicular nuclei containing one or more nucleoli. An occasional cell is met in which the nucleus is in some stage of karyokinesis. These large

cells can be readily detected by numbers of minute, highly refractive fat droplets embedded in the protoplasm. Under high power, besides the nucleus the large phagocytic elements are found to contain within their protoplasm numbers of cell inclusions presenting the appearance of vacuoles containing central bodies. Each cell usually contains several of these inclusions, and in some cases the protoplasm is closely packed with the inclusions and fat droplets. Numbers of the inclusions present the appearance of the spores of Plasmodiophora when examined in the fresh state, i. e., spherical, greenish-yellow bodies of high refractive index, with a highly refractive central body. The derivation of the inclusions first mentioned from the typical spores of the organism can be readily traced. In the younger tumors the fresh scrapings show the presence of large numbers of leucocytes. Careful examination of the leucocytes shows that spores or inclusions within the leucocytes are extremely rare. In only one case have we found a spore within a leucocyte.

Sections through the surrounding tissue and the implanted vegetable tissue were hardened in sublimate, formalin and Hermann's fluid. Preparations hardened in Hermann and stained with Plimmer's method gave the most satisfactory results. An examination of growths of ten days or under reveal the following relations: The outline of the plant structure is well preserved and the relations of the contained spores and the remains of the amœbæ can be easily determined. At the margins the plant tissue is surrounded by a mass of coarse granulation tissue, more or less densely mixed with polymorph nuclear leucocytes. In uninfected cases the leucocytes are seldom present after the twelfth day, as pointed out by Podwyssozki. An examination of the plant tissue reveals the spores intact within the infected cells. In preparations from which the osmic acid has not been removed, the spore presents a characteristic appearance. Instead of the diffused blackening which characterizes the spore in the fresh state, in many spores the fat is gathered together in globules at the center. (See Fig. 11.) At the margin of the plant tissue the spores can be traced for a certain distance into the granulation tissue by the blackened droplets of fat which they contain. It is evident by study-

ing the margin of the preparation that the spores rapidly lose their fat, whereupon they can no longer be distinguished in preparations stained with safranin. In preparations from which the osmic acid has been removed and the section stained with iron hæmatoxylin and neutral red (Plimmer's method) the chromatin of the spores stains a blue-black, and in the spores remaining in the plant tissue is irregularly arranged near the center of the spore. At the margins of the plant tissue the spores can be detected in the elements of the granulation tissue surrounding it. This tissue is made up of large connective tissue phagocytes with vesicular nuclei of varying size. The nuclei stain deeply and contain one or more nucleoli. The protoplasm is finely granular. In these cells the spores of the organism can be demonstrated, although in preparations from the tenth day on many show marked alterations in appearance. In early implantations the spores are readily recognizable, still containing chromatin and presenting the appearance found in the spores included in the plant tissue. The large phagocytic cells contain usually one or more. In some cases the protoplasm is filled with closely packed spores. In tumors from the twelfth day on many of the spores within the cells are found to have increased in size. The chromatin is usually absent and the protoplasm is contracted in the form of a central body surrounded by a clear space. (Figs. 12 and 13.) The periphery of the spore is indistinguishable from the protoplasm of the cell containing it, and the whole presents an appearance closely resembling certain cell inclusions in cancer.

The condition of the amœbæ within the plant tissue after implantation in the subcutaneous connective tissue of animals is worthy of especial attention. *In all preparations we have found that the amœbæ and all forms of the parasite,* with the exception of the spores, *have disintegrated.* The site of these forms is marked by masses of disintegrated protoplasm and chromatic material. By a careful comparison of portions of the plant tissue in each case before implantation, we have been able to determine that this is actually what occurs. The infection of the surrounding tissues is therefore owing to the presence of the spores, and the amœbæ are undoubtedly incapable of producing infection. This is shown by the cases in which we implanted fragments of young clubroot in which the organism had not

PLATE XI.

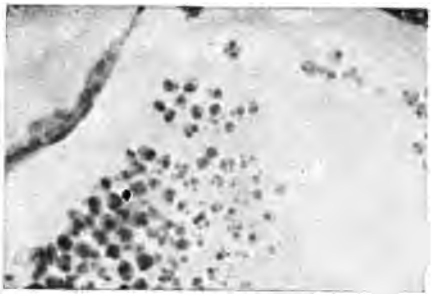

Fig. 11.

Fig. 12.

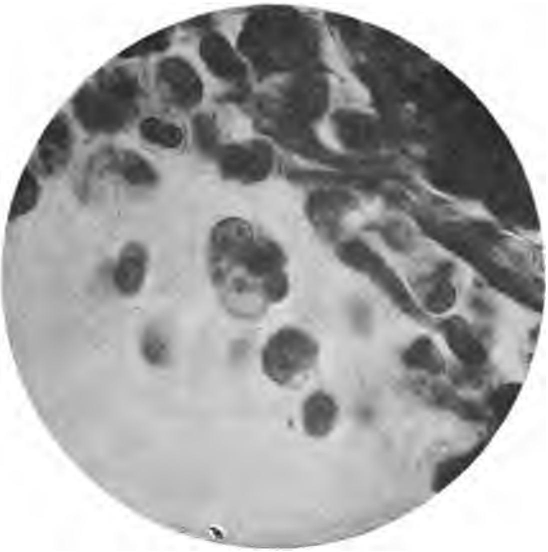

Fig. 13.

reached the stage of spore formation. In all of these experiments the fragment of plant tissue acted simply as a foreign body in the tissue, and after the usual period disintegrated and was removed. Macroscopically these cases could be readily distinguished from those in which the plant tissue contained spores, in which case granulation tumors the size of a hazelnut invariably developed. It is *highly probable in this case that the amœbæ perished with the plant cell, in which case the symbiosis referred to by Nawaschin is apparently complete.*

The nodules which result from the infection of warm-blooded animals by the spores of Plasmodiophora disappear in a period varying from six weeks to three months. They are therefore not malignant, the organism being ultimately destroyed by the activity of the cells in which they are found.

Our second series of experiments, in which we employed frogs, presented even more definite characteristics than those found in warm-blooded animals. In these experiments the necessity for preventing the introduction of bacteria was not as great as in the warm-blooded animals. The frog is apparently capable of overcoming bacterial infection with readiness. In these experiments the club-root was ground in a mortar in sterile salt solution. After determining that spores were present in the material it was strained through cheese-cloth to remove the coarse fragments of plant and then injected into the peritoneal cavity with a hypodermic syringe. Frogs examined at the end of seven to ten days show upon the surface of the peritoneum, especially in the omentum, whitish firm nodules, varying in size from a pinhead to a grain of rice and larger. In some cases the omentum is thickly infiltrated with larger and smaller nodules. Teased preparations from these nodules and scrapings show that they are composed of large endothelial cells containing spores of Plasmodiophora, and in scrapings made from the periphery of the nodules large numbers of coarsely granulated elements can be found. In frogs killed after the fifteenth day the granulated cells are greatly decreased in number. The granulated cells were never found to contain the spores of the organisms. The nodules were hardened in formalin, sublimate and Hermann's fluid.

Preparations hardened in sublimate and Hermann were best suited for the investigation of the spores, which in the formalin preparations were scarcely distinguishable. In sections hardened in sublimate and stained with hæmatoxylin-eosin the structure of the nodules is well-defined. It consists of accumulations of large cells with large vesicular nuclei of varying shapes. Many of the cells are oval, the majority are fusiform. (Fig. 14.) They are closely packed and in many cases arranged about centers, presenting an appearance not unlike the pseudo-pearls or whorls found in certain endotheliomata. (Fig. 15.) The nuclei are rich in chromatin; the cell protoplasm stains readily with eosin. On the surface of the smaller nodules which lie directly beneath the peritoneum the superficial endothelium can be readily distinguished from the cells of the nodules. The nodules frequently lie in the neighborhood of blood vessels, and from their relation have apparently developed in the sub-peritoneal lymph spaces. About the margins of the nodules the connective tissue stroma is densely infiltrated with polynuclear eosinophiles. (Fig. 16.) The cells forming the nodules can be readily distinguished in the connective tissue cells of the stroma. At the margins of the larger nodules the cells forming them penetrate into the surrounding stroma, in which they form cell nests sharply delimited from the surrounding connective tissue. Frequent karyokinetic figures are found within the nodules which have never been detected in the surrounding connective tissue. (Figs. 17 and 18.) In preparations stained with hæmatoxylin eosin the spores of Plasmodiophora are scarcely discernible. The protoplasm of the cells at the centres of the nodules presents a coarse granular appearance, and is apparently filled with rounded bodies of indefinite form which occasionally stain a pale rose tinge with hæmatoxylin. As will be seen by the further examination of preparations, these bodies are the spores of Plasmodiophora. In formalin preparations the spores are still more poorly defined and would undoubtedly escape notice. It is probable that by the use of this fixative Behla failed to detect the spores of the organism in infected cells.

In sections from material hardened in osmic acid, from which the osmic acid has not been removed, counterstained with safranin, the

Plate XII.

Fig. 14.

Fig. 15.

Plate XIII.

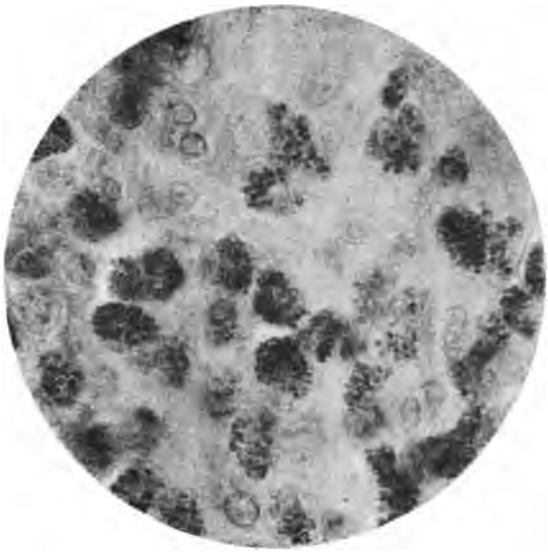

Fig. 16.

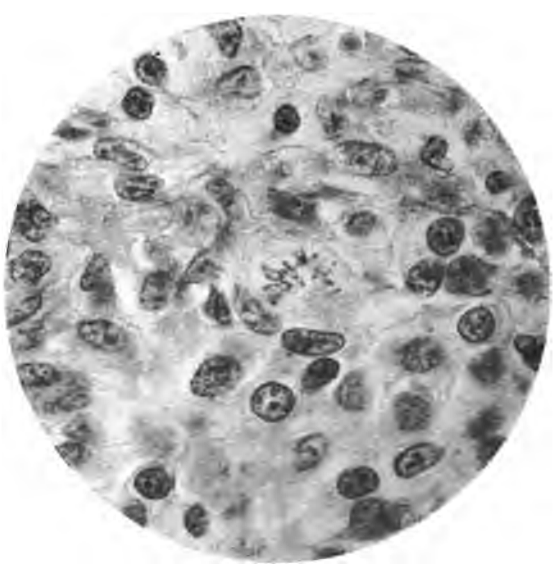

Fig. 17.

Plate XIV.

Fig. 18.

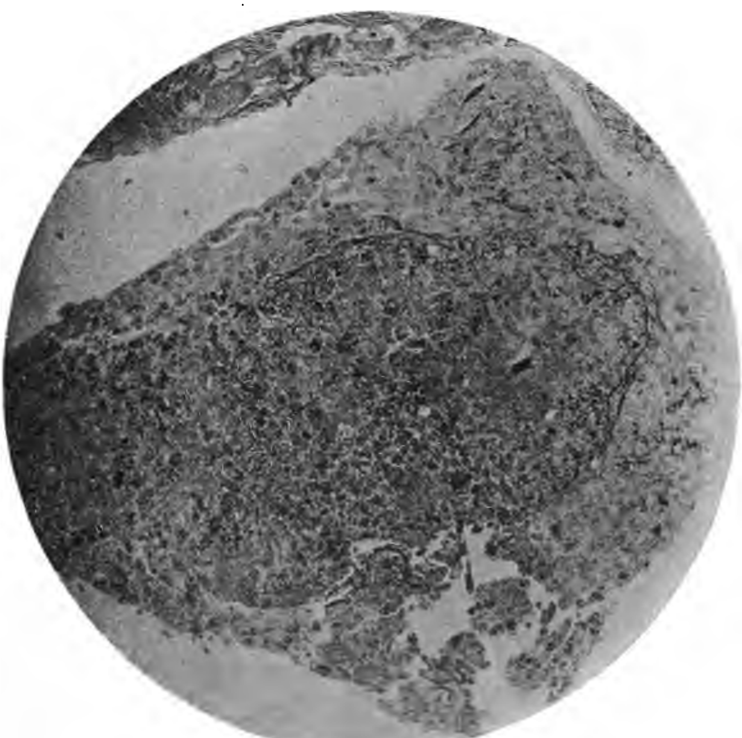

Fig. 19.

PLATE XV.

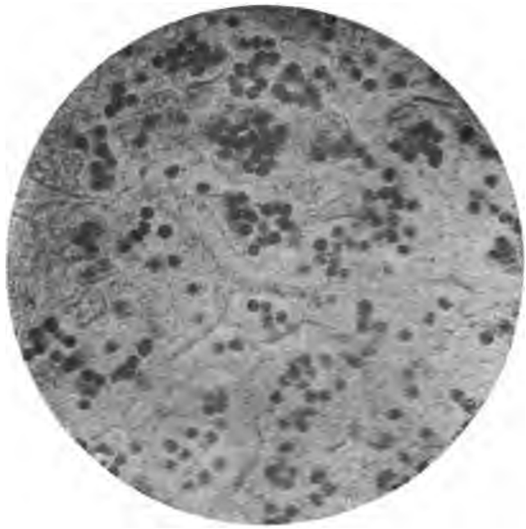

Fig. 20.

Fig. 21.

PLATE XVI.

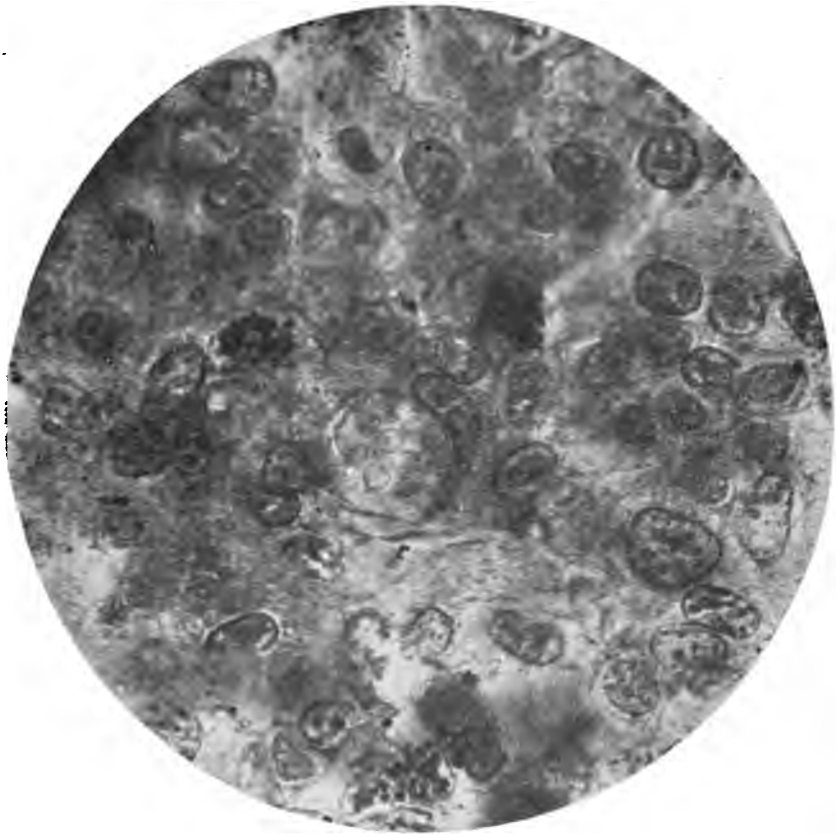

Fig. 22.

Fig. 23.

PLATE XVII.

Fig. 24.

Infected Fig. 25, after Woronin. Normal

Fig. 26.

spores of the organism within the cells of the nodules can readily be detected as blackened, spherical bodies, approximately three micromillimeters in diameter. Under low power (see Fig. 19) the spores present the appearance of fat droplets blackened in the usual way by the osmic acid within the cells. They are most densely arranged at the centers of the nodules, the cells at the periphery containing a fewer number of spores than those forming the center. Under high power (Fig. 20), the fat is found to be most densely arranged about the periphery of the spore, and many spores are found which apparently contain no fat whatever. These shadowy forms, many of which apparently contain no internal structure, look like minute shadowy red blood corpuscles. In preparations hardened in sublimate and stained with Plimmer's method the picture presented is similar to that found in the hæmatoxylin-eosin preparations, with the exception that the nuclei are more sharply defined and many of the spores are found to contain chromatin. The differentiation of the cells of the nodules from the subperitoneal connective tissue stroma is more sharply defined. Karyokinetic figures are likewise more pregnantly stained and are found to be quite numerous. The characteristic nest-like arrangement of the endothelial cells is likewise clearly defined. (Fig. 14.) The granules of the eosinophiles of these preparations are capriciously stained, in many cells unstained, in others distinctly blue. The finer structures of the spores are best observed in preparations hardened in Hermann's fluid and stained with iron hæmatoxylin and neutral red. (Fig. 21.) In these sections it can be seen that many of the spores have lost their chromatin, while the majority possess an irregular chromatic structure at the center of the spore separated from the delimiting capsule by a narrow space. Many of the spores are entirely free from chromatin, and in some the chromatin is arranged about the periphery of the spores in the form of fine granules of uniform size. In a few cells we have seen structures of approximately five micromillimeters in diameter sharply defined from the protoplasm of the cell, containing uniform granules, staining deeply with the nuclear stain. These forms are rare and we believe them to be derived from the spores. Whether they represent a stage of

further development or retrograde changes in the spores it is impossible to determine. Free chromatin granules of this type are likewise occasionally encountered, especially about the peripheries of the nodules. Occasionally spores are encountered which have increased in size, which are free from chromatic material, with an irregular, or spherical central body, again presenting an appearance closely resembling the cell inclusions of carcinoma. The granules of the granulated cells in these sections stain deeply with the iron hæmatoxylin. It is difficult to determine in many cases whether one is dealing with the minute spherical elements apparently derived from the spores, or free granules from these cells. In regions in which the granulated cells are abundant the differentiation is often impossible. A few sublimate sections were stained with Biondi-Heidenhain for the purpose of determining the affinity of the granules of these cells, which were found to stain a brilliant orange. A certain number of the larger endothelial cells near the centers of the nodules were found to contain great numbers of spores. In many cases their protoplasm was greatly distended and the spores were closely packed in large vacuoles presenting an appearance not unlike a cyst filled with spores. Fig. 22 represents a cell of this description from a section stained with Biondi-Heidenhain. The appearance of the spores in these cells is so like illustrations in the recent publication of von Leyden of inclusions found in carcinoma of the lung that the two should be viewed together. (Fig. 23.) The tendency of the cells of the nodules to coalesce often leads to the formation of giant cells. In one of our preparations giant cells with the spores arranged about the nuclei were occasionally encountered. The relation of the spores to the nuclei of the cells is often of interest. *In many cases, especially in the smaller cells composing the nodules, the nucleus of the cell will be found to be pushed to one side and curved about the spore, giving it an appearance closely representing certain illustrations of centrosomes.* In the giant cells the spores are commonly arranged about the nuclei, the center of the giant cell being free. (Fig. 24.) In sections stained with Mallory's connective tissue stain the cells of the nodules stain a brilliant red or orange, whereas the connective tissue stroma stains a brilliant blue.

Fine fibres of connective tissue can be found extending into the smaller nodules, but the larger nodules are, for the most part, free from stroma, except about the margins where the cells of the nodules infiltrate the surrounding connective tissue structure from which they were sharply defined.

Frog III, killed after 47 days, shows upon the surface of the liver the mesentery and omentum, nodules varying from the size of a pinhead to that of a large grain of rice. These are firm and white and of a little greater consistence than those found in Frog I. Fresh examination shows these nodules to be composed for the most part of large, spindle elements in which an occasional vesicular structure, varying in size from three to six micromillimeters, can be found. Many of these vesicular structures contain central bodies which are undoubtedly spores of Plasmodiophora. In sections hardened in sublimate and stained with hæmatoxylin-eosin the tissue of the nodule is found to be composed of large spindle elements with vesicular nuclei. Viewed under low power these cells are seen to be arranged about centers, presenting an appearance like the whorls of cells found in certain sarcomata. Occasional giant cells are present, measuring as high as 30 micromillimeters in greatest diameter. These contain many nuclei, as many as 18 or 20 being counted in one cell. These are usually arranged about the periphery of the cell or in a group at the center. Careful examination of the preparation for spores shows that occasional cells contain shadowy spherical bodies, usually without other structure, but occasionally with a central body. Many of these spores are as large as six micromillimeters and present the characteristics of intracellular inclusions found in carcinoma. Occasionally a granulated cell can be found at the margin of the nodules. The cells of the nodules do not stain as deeply as those of Frog I, and the intracellular connective tissue stroma is more prominent. Embedded in one of these nodules are two cystic structures of spherical outline measuring eight micromillimeters in diameter. Their margins present a beaded or radiating appearance, and each contains a mass of unstained protoplasm of irregular form, nearly filling the cyst cavity. The appearance of these structures is so striking as to leave absolutely no doubt that they *represent the spore*

cysts of Plasmodiophora with well-developed swarm spores within them.

From these experiments it will be seen that the spores of Plasmodiophora, when injected into animals, are capable of causing granulomata composed largely of endothelial cells which present certain characteristics distinguishing them from the ordinary infectious granulomata, and which give them an appearance more closely resembling endothelioma and sarcoma than the granulomata usually encountered. From a careful survey of our preparations we are able to confirm the conclusions of Podwyssozki given on page 27, and further to add that the observation in Frog III of perfectly developed spore cysts inclosing what seem to be well-developed swarmers shows that the organism is capable of development to this stage within the tissues of cold-blooded animals. These nodules, as stated by Podwyssozki, ultimately subside and resemble endotheliomata only in their histological characteristics. The spores, both in warm and cold-blooded animals, undergo certain alterations in the tissue, after which they closely resemble certain of the bird's-eye inclusions in malignant tumors.

The large numbers of eosinophiles noted about and in the nodules in the animals infected with spores of Plasmodiophora call to mind the similar accumulations found in the lymphomata of Hodgkin's disease. The spores of Plasmodiophora in the tissues of both warm and cold-blooded animals correspond in size and appearance very closely to certain structures described by Flexner* in lympho-sarcoma which he suggested were protozoa. It is possible that a further investigation of Plasmodiophora and allied organisms may throw light on the nature of the spherical bodies described by the above author.

The analogy between clubroot and cancer.—The application of the facts pertaining to the distribution of the amœboid form of Plasmodiophora in clubroot, as determined by Nawaschin, to the nature of the proliferation of the cancerous epithelium as it is now under-

*Multiple lympho-sarcomata, with a report of two cases. A contribution to the infectious nature of lympho-sarcoma. *The Johns Hopkins Hospital Reports*, Vol. III, 1894, p. 153.

stood in man, reveals the following status: The outgrowths of clubroot are the result of proliferation and hypertrophy of the cells of the cortex. The cells of the medullary portion of the plant are never infected. Inasmuch as the infection of the plant can occur during any stage of its development, this must be attributed to a selective faculty on the part of the swarm spores at the time of their entry into the plant tissue. Examination of sections of young clubroot in which the amœboid is the predominating form of the organism discloses the characteristic arrangement of the infected cells as pointed out by Nawaschin. A similar distribution can be found in the beautiful illustrations of Woronin. (Fig. 25.) The infected cells are in every case arranged in groups, and serial sections show that each infected cell is at some point adjacent to another infected cell, the whole group surrounded by hypertrophic cells in which no parasites are to be found. This peculiar arrangement of the cells and the fact that the amœbæ have never been detected in the act of penetrating the wall pits of the cells has led Nawaschin to the conclusion that the *distribution of the parasites is owing exclusively to the proliferation of one or more primarily infected cells.* That he has found dividing plant cells containing amœbæ and that the amœbæ are in this way distributed is beyond doubt. The distribution of the groups of infected cells throughout the cortex is undoubtedly the result of multiple infection. An examination of the hypertrophic cells of the cortex surrounding the groups of infected cells, but free from parasites, reveals the presence of an occasional karyokinetic figure. From this it would seem that the amœbæ, themselves incapable of penetrating from one cell to another, liberate some soluble toxic substance which, diffusing into the surrounding cells of the cortex, leads to hypertrophy and occasionally to proliferation. This toxic agent, whatever its nature, is likewise capable of causing proliferation of the cells forming the vessels of the plant, which in some cases proliferate to such an extent that in the neighborhood of the infected cells they are frequently tortuous, coiled and otherwise distorted. This condition is admirably shown in Fig. 26, from Woronin. In no case have parasites been found within the cells of the vessels. On examination of sections of clubroot in which the

amœbæ have passed through the plasmodial phase terminating in spore formation, it will be noted that the hypertrophic character of the surrounding parenchyma cells has largely disappeared. It would thus seem that the toxic action of the parasite is confined to the vegetative stage. The proliferation of the cells in the tumor can therefore be divided into two classes: first, infected cells; the stimulus for the division in this case is probably toxic, but the proliferation is no doubt for the purpose of throwing off the parasite, which is seldom successful, as the amœbæ proliferate much more rapidly than the host cell, and by the time the process of proliferation is terminated in the plant element, the entire cell being filled with amœbæ, a certain number remain in each of the daughter cells formed by the division. The second order of proliferation is that affecting the surrounding structures. This is purely toxic and appears to subside when the proliferative phase of the organism terminates. This affects the adjacent cells of the cortex and the cells of the vascular system. If fragments of clubroot containing amœbæ are transplanted upon the cortex of an uninfected plant of the same variety, a tumor will develop which is the result of proliferation of the infected transplanted cells, combined with hypertrophy and a certain amount of proliferation in the surrounding parenchyma cells of the plant upon which the infected cells have been implanted. There is no doubt whatever, if cells of the tumor in the first case could be selected which contained no parasites, no tumor formation would result in the inoculated plant. It will thus be seen that in order to produce clubroot by inoculation infected cells must be transplanted. In this case likewise both cell and parasite must be transplanted intact. Attempts to produce inoculation tumors in plants with the amœbæ alone have thus far proved negative, and so far as our present knowledge extends, a primary infection can only be induced by the introduction of the flagellate form of the organism after the germination of the spores in the earth. The endothelial connective tissue tumors which result in animals from the implantation or inoculation of the spore form of Plasmodiophora from the plant, are probably largely the result of toxic substances contained within the spore, acting upon the cells of the animal. The transient leucocy-

tosis likewise strongly suggests this explanation. As the organism is incapable of accomplishing a reproductive cycle when implanted under these conditions, the process is not progressive, although the spores are found shortly after implantation embedded in the cells which have proliferated about them.

The frequent occurrence of karyokinetic figures in the cells of the animal forming these tumors indicates that the mere presence of the spores is capable of inducing proliferation of certain elements in the animal. It must be noted that this toxic activity of the spores is exerted in a selective way. The cells surrounding the implanted spores, with the exception of the primary (transient leucocytosis) are all of one character and apparently derived from one source. Instead of a heterogeneous mixture of elements, such as we find in granulation tissue, these nodules are all of the same type, and in the frog present an appearance in the progressive stage closely resembling endothelioma.

If in the light of the ascertained facts governing the relation between Plasmodiophora and the plant cell, as above stated, we turn to the conditions as we find them in cancer in man and animals, a series of analogies can be developed which indicate that in Plasmodiophora we have a parasite, the cause of a specific tumor, which in its relation to the tissue which it infects fulfils many of the conditions which must be required of a parasite before it can be accepted as bearing a direct etiologic relation to cancer. The investigations of Hauser, Peterson and others have demonstrated that in primary epithelial growths a direct continuity with the epithelium from which the tumor is derived can be readily traced. This has been accomplished by means of serial sections and wax models. These investigations have likewise shown, especially in epithelioma, a form of tumor which has been most frequently subjected to this form of examination, that the proliferation frequently begins at several points, as a rule not far distant from one another. Starting at these points the tumor spreads into the surrounding structure and through the medium of the lymph spaces, carcinomatous cells are carried into the circulation, when the phenomenon of metastasis formation supervenes.

Associated with the proliferation of the epithelium is with rare exceptions a reaction of the adjacent connective tissue. This is evidenced by the well-known round celled infiltration at the margins of many carcinomata, by the extensive development of a connective tissue stroma and by the frequent appearance of karyokinetic figures in the nuclei of the connective tissue elements forming it. The evidences of mitosis in the stroma of the tumor are never so frequent as in the proliferating epithelium of the tumor proper. The structure of the newly formed stroma of the tumor likewise includes a more or less well-developed vascular system. That the specific factor of the tumor formation is not in the stroma is evidenced by the fact that metastatic connective tissue proliferation is not a phenomenon of the dissemination of carcinoma. On the other hand, in the regions where metastases from the primary tumor develop without regard to the tissue or organ in which this occurs a stroma derived from the adjacent connective tissue results from the presence of the epithelial elements of the tumor. It is thus seen that the epithelial elements carry with them and elaborate some agent capable of inducing not only the primary reaction of the connective tissue as expressed by the frequent round-celled infiltration at the margin, but an extensive proliferation of the connective tissue structure which, both in the primary tumor and in the metastases, leads to the development of a more or less well-defined connective tissue framework which forms no inconsiderable proportion of the new growth. It is generally conceded that the cells of carcinoma in a given case are derived by proliferation from groups of cells which have primarily undergone the cancerous transformation. In most cases the cell, once so transformed, proliferates indefinitely, and transported through the medium of the circulation to other regions of the economy, continues its proliferative activity, and in this way the metastases are formed.

It is, however, a well known fact that every cancer cell is not capable of proliferating indefinitely. This is first shown by the large number of cells which present high grade degenerative changes, in many cases the forerunners of complete disintegration. It has likewise been noted that all tumor elements are not capable of producing

metastases, even when transported under exactly the conditions ordinarily leading to this result. For instance, cancer cells have frequently been found in the pulmonary capillaries and in the ductus thoracicus, regions in which metastases frequently develop but which show no evidence of proliferation, although present in large numbers. It will thus be seen that every cancer cell is not capable of continuing indefinitely the cancerous process.

Inasmuch as in clubroot we have no metastases, the outgrowths in this case could at best only be compared with the primary tumor in cancer. We have seen that the tumor in clubroot is composed of cells containing parasites and hypertrophic cells immediately adjoining them. The infected cells when transplanted are capable of continuing the growth. The hypertrophic cells, which in all other respects closely resemble them but which contain no parasites, are naturally incapable of producing an infection. We have seen, by analysis, that the primary growth in cancer presents a certain analogy in that it is composed of cells capable of continuing the proliferation when transported to distant regions, and other cells which morphologically closely resemble them, which are incapable of producing metastases. *For this reason we must conclude that if a parasite were the basis of the cancerous proliferation, it would not necessarily be present in every epithelial cell forming the tumor.* It must necessarily be seen that the cells which are incapable of continuing proliferation must either contain no parasites or have reached a stage in which it is itself incapable of further proliferation, in which case the organism has in all probability passed into some permanent spore-like form, a condition in which it would be incapable of reinfecting epithelium or other cells of the organism without passing through some ectogenous cycle of development. This is exactly the case in Plasmodiophora, and it may be pointed out that cell inclusions in cancer, which are held by certain investigators to be of parasitic nature, are not present in all the cells even when most frequent. To this must be added, however, that the inclusions in cancer which so closely resemble the amœboid form of Plasmodiophora at best represent but one form of the parasite; that at least occasional spores must

be accounted for, and that the organism on its entry into the epithelium is probably present in some form which, with our present methods, we are unable to recognize. The fact that the swarm spores of Plasmodiophora when injected into the tissue, so closely approximate in their appearance certain normal tissue elements that they are unrecognizable, indicates that such a supposition is reasonable.

As the specific factor in cancer, having once developed in certain cells, remains identified with them, being handed down through proliferation of these cells, it must greatly increase in amount. It has been suggested that this specific factor is of a toxic nature, but no explanation has been offered as to how a small amount of toxin, starting in a few cells, can continually reproduce itself. From what we know at present of toxins there is absolutely no ground for this supposition, and even in the case of enzymes or ferments, which are sometimes referred to, we have nothing analogous to the conditions in cancer. There is no doubt that the development of the stroma in cancer must be attributed to the action of a toxin since this action is local and undoubtedly results from the presence of the cancer cells, but inasmuch as the mere proliferation of normal cells does not lead to the elaboration of a toxic substance, we must assume that this toxic substance is directly associated with the essential factor which causes the cancerous transformation of the epithelium. As the essential factor in cancer increases with the proliferation of the cells, or in other words, reproduces itself, and we know that no toxin is capable of this, we arrive at the conclusion that the presence of an organism in the epithelium offers the best explanation of the phenomena as they occur. An organism of the protozoan group, especially one more or less distantly related to the Mycetozoa, and therefore comparable to Plasmodiophora, would best fulfil these conditions. That such organisms upon infecting the tissue elements of a higher animal do, in all probability, elaborate toxic substances is shown by the facts in Plasmodiophora. A similar state of affairs has been described by Pianese, who observed atypical karyokinetic figures in the epithelial cells of the urinary tubules of the guinea-pig which were infected by a protozoan parasite.

We have seen that in Plasmodiophora the parasite divides until the demands upon the cell are such that it likewise divides. This continues until by repeated divisions the parasite has completely filled the cell and exhausted the nourishment, whereupon the organisms are transformed into permanent spores. These spores are incapable of reinfecting the cells of the plant until they have passed through the ectogenous cycle, in which they lie during the entire winter in the ground, liberating swarm spores with the advent of spring, which, entering fresh plants, lead to reappearance of the disease.

The infection in Plasmodiophora destroys the growth of the plant, and in a certain sense may be looked upon as a malignant infection. It is seen that the organism remains in the amœboid stage and in a state of symbiotic existence with the host cell until it is exhausted. This is dependent upon the relative rate of proliferation. It is possible to conceive that in cancer the greater proliferative power of the epithelial cell might place it on a footing with the parasite, which would enable it to proliferate rapidly and indefinitely, in which case only exceptionally unfavorable conditions would lead to the development of spores. These spores, even if present in the tissue, would be incapable of infecting uninfected cells without passing out of the organism and through some ectogenous cycle. They would likewise be incapable of infecting the tissue cells of other animals or individuals when transplanted without the interposition of this cycle, as is the case in Plasmodiophora.

The parasite, once having entered into this symbiotic relation with the cell, would perish with the cell unless it had taken on the permanent spore formation just mentioned. For this reason it would be impossible to produce tumors even in animals of the same type without the transplantation of both cell and parasite, which applies both to the transplantation experiments as carried on in animals and the relations as they exist in Plasmodiophora. The few cases in which inoculation of animals with peritoneal fluid from man has been followed by epithelial proliferation cannot be compared directly with the conditions as they occur in nature. In the first place, while these tumors closely resemble malignant epithelial tumors as we find them in man and animals, they have in no case proved truly malignant;

have never led to metastasis, and have ultimately been overcome by the animal. They may fairly be compared to the endothelial nodules which develop in frogs around the implanted fragments of clubroot. The conditions in this case are entirely abnormal, and the organism at best passes through but a portion of the necessary cycle. The nodules obtained in the liver of a dog by intravenous injection of peritoneal fluid from cancer of the peritoneum in man indicate the correctness of this explanation of these rare occurrences.

In conclusion it may be fairly stated that there are inclusions in cancer which, viewed in the light of Plasmodiophora, are best explained as parasites; that a comparison of the conditions found in clubroot with those found in man show that we are now acquainted with a parasite capable in many ways of fulfilling the conditions required of a parasite for cancer. Our efforts should therefore be directed to the more accurate determination of the nature and distribution of this too little known class of organisms, and to the determination if possible of an ectogenous cycle for the parasite of cancer, which includes the possibility of an intermediary host.

February 1, 1903.

ON THE EVIDENCE OF NUCLEAR DIVISION OF CERTAIN CELL INCLUSIONS (THOMA, SJÖBRING, PLIMMER'S BODIES) IN CANCEROUS EPITHELIUM.

BY HARVEY R. GAYLORD, M. D.

Since the advent of cellular pathology the attention of investigators has been directed to certain bodies embedded in the cytoplasm of the cells of malignant tumors. The difficulty of determining the nature of these inclusions is well evidenced by the extensive literature pertaining to the subject, but which even to-day leaves the significance of at least a number of these structures in doubt.

The bodies with which we wish to deal in this paper are spherical or slightly oval structures, from .004 to .01 mm. in size, or in exceptional cases of still greater dimensions. They invariably contain a small body, usually centrally placed. With the exception of this central body the resting inclusions present an appearance not unlike that of a vacuole, as no structure other than the central body is demonstrable. The entire structure is embedded in the protoplasm of the cancer cells and, where the body is of greater dimension, the cell nucleus is commonly pushed to one side and curved about it. The staining reaction of these inclusions is dependent largely upon the fixative employed. In material hardened with formalin and stained with Delafield's or iron hæmatoxylin, the central bodies of a certain number of the inclusions take the nuclear stain. Where osmic acid is used as a fixative, in which case the inclusions are most definitely demonstrated, the central body of the inclusions stains as does the protoplasm. These bodies may be found unstained in fresh material directly after removal of the tumor.

Although, as will be seen from the historical review, these bodies have been repeatedly observed and in many cases accurately illus-

trated, they have in recent times through the exhaustive article of Plimmer attracted renewed interest. In several of the recent publications on the subject, the bodies have been spoken of as "Plimmer's bodies." Von Leyden, one of the most recent writers on the subject, has called attention to their similarity in appearance to the eye of a bird, for which reason they are coming more and more to be spoken of as "bird's-eye inclusions," a not inapt expression.

Historical.—On review of the literature it becomes evident that many observers have seen and illustrated the inclusions above described. As early as 1847, in the first volume of Virchow's Archiv, is found an article by Virchow, entitled "Zur Entwickelungsgeschichte des Krebses, nebst Bemerkungen über Fettbildung im thierischen Körper und pathologische Resorption," in which on Plate II, Fig. 5, the cells shown at *a, g, i, l, n,* and *k* undoubtedly contain inclusions of this nature. It is interesting to note that the author represents cells in the fresh state. Virchow regarded these bodies as modifications of the nuclei of the cancer cells.[1]

In Vol. III of Virchow's Archiv (Die endogene Zellenbildung beim Krebs), Virchow further describes cell inclusions, of which those illustrated on Plate II, Figs. 2*c*, 4*a*, 2 and *d*, appear to represent bird's-eye inclusions, although the illustrations are not sufficiently characteristic to remove a possible doubt. (See Fig. 1.)

Soudakewitsch[2] in two articles published in 1892, gives repeated illustrations of these bodies. Plate V, Fig. 6, carcinoma of breast, represents a body apparently undergoing division with four central bodies arranged in the form of a cross. Fig. 2, Plate VI, also carcinoma of the breast, shows multiple inclusions, the one above and

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[1]The cell inclusions described by Langhans in *Deutsche Chirurgie von Billroth und Lücke*, 1886, in the epithelial cells of carcinoma of the glands of Kupfer, do not belong under this heading, although Lubarsch (*Pathologische Anatomie und Krebsforschung*) wishes so to classify them. The bodies described and illustrated by Langhans are round, well-defined bodies, from the size of a nucleus to that of a large vacuole. They were, however, filled with granular material and surrounded by deeply stained membranes. Many of them were drawn out in tubular or branching form. It will be seen that this description in no way conforms to that of the bird's-eye inclusions.

[2]Soudakewitsch.—Recherches sur le parasitisme intracellulaire, etc. *Annales de l'Institut Pasteur*, 1892, March 25, No. 3.

to the right presenting a definite phase of division. (See Fig. 2.) Fig. 27, Plate VI, carcinoma of the breast, hardened in Fleming and stained with safranin, represents a resting body. Plate VII, Fig. 17, carcinoma of the pancreas, hardened with osmic acid and stained with hæmatoxylin, represents a rosette form. Fig. 19 represents a cell with multiple inclusions from the metastases of cancer of the pancreas. In a second article in August of the same year he describes further inclusions. That of Fig. 7, Plate XII, from a primary case of carcinoma of the pancreas, illustrates seven definite inclusions, with central bodies forming a rosette. (See Fig. 2.) Fig. 15, from a primary carcinoma of the liver, stained with osmic acid and hæmatoxylin, represents a group of these bodies, and in Fig. 17, a body undergoing division is represented from a carcinoma of the pancreas. (See Fig. 2.) Fig. 21 again represents a group of similar inclusions from a case of cancer of the liver.

Sjöbring[1] gives a most accurate and consistent description of bird's-eye forms of inclusions. In Figs. 1, 12 and 14 he illustrates characteristic forms. (See Fig. 3.) Thoma[2] describes bodies somewhat similar to those of Sjöbring. His original article is unaccompanied by illustrations. Illustrations given in his Lehrbuch f. path. Anatomie, 1894, p. 169, leave some doubt as to their identity. Fig. *a* apparently represents a bird's-eye inclusion, and those shown in the large figure above likewise appear to be of this nature. Figs. *c* and *d* of this illustration, representing a form of division, do not coincide with any forms we have personally observed. (See Fig. 4.)

An investigator who undoubtedly observed these bodies was P. Foa.[3] (See Fig. 5.) In Figs. 2 and 16 of Plate II and 13 of Plate III, this author illustrates these bodies from carcinoma of the breast. He also recognizes the identity of many of the bodies described by him and those of Soudakewitsch, just mentioned.

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[1] Sjöbring.—Ein parasitäre Protozoartiger Organismus in Carcinomen. *Fortschritte d. Medecin,* 1890, p. 529.

[2] Thoma.—Ueber eigenartige parasitäre Organismen in den Epithelzellen der Carcinome. *Fortschritte der Medecin,* 1889, p. 413.

[3] Foa.—Ueber den Krebsparasiten. *Cent. f. Bakteriologie,* Vol. XII, p. 185, 1892.

Kürsteiner[1] describes two cases of carcinoma, one villous carcinoma of the bladder, and the other papillary adenocarcinoma of the uterine mucosa, in which he found embedded in the cells spherical and oval bodies with well-defined central structures staining with eosin. His illustrations are all taken from a villous carcinoma of the bladder and leave no doubt that in Figs. 3, 4, 5, 6, 7 and 8, Plate XII, he was dealing with typical bird's-eye inclusions. (See Fig. 6.) Of interest are the large number of inclusions which Kürsteiner noted in certain cells of his preparations. In one cell he was able to count as many as *eighty inclusions.* He inclines to the belief that the inclusions may be parasites, but expresses himself with great caution.

Seegenbeck van Heukelom,[2] in an address before the 10th National Medical Congress in Berlin, 1890, describes the presence in carcinoma, including nearly every type, covering some 200 different cases, of large and small spherical inclusions in carcinoma cells. These sometimes presented a double contour, appeared to be filled with protoplasm and presented a nuclear-like structure, which stained with carmine. Besides these so-called larger spheres he describes smaller ones, which he says were found embedded in the protoplasm and in the nuclei. They did not stain with carmine, and but weakly with eosin. They were not very refractive. From his description of the larger bodies, it is certain that they corresponded with those of Wickham, and of the smaller it is difficult to say whether they represent the typical bird's-eye inclusions or not. The description is, unfortunately, unaccompanied by illustrations.

The description given by Podwyssozki and Sawtschenko[3] varies somewhat from the description of other authors, but some of the inclusions illustrated by them present the characteristics of the typical bird's-eye form. Fig. 2, Plate VII; Fig. 20, Plate VIII, inclusion to the left, are characteristic. (See Fig. 7.) The tech-

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[1] Kürsteiner.—Beiträge zur pathol. Anatomie der Papillome und papillomatösen Krebse von Harnblase und Uterus. *Virchow's Archiv,* Vol. CXXX, p. 463.

[2] Seegenbeck van Heukelom.—*Centralblatt f. allg. Pathologie und pathologische Anatomie,* Vol. I, p. 204.

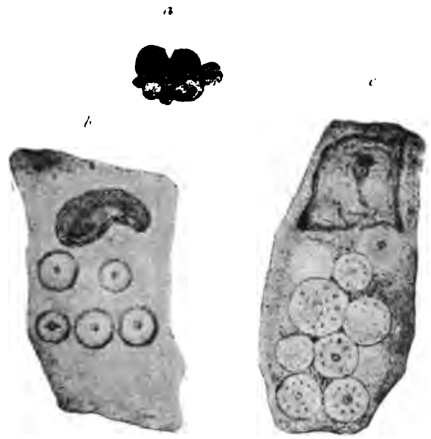
[3] Podwyssozki and Sawtschenko.—*Centralblatt f. Bakteriologie,* Vol. XI, No. 16, 1892, p. 493.

Plate XVIII.

Fig. 1.

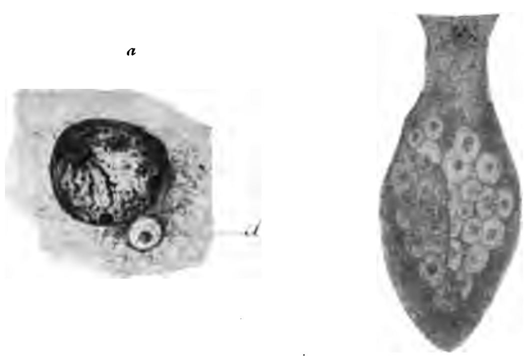
Plate II, Fig. 4*d*, after Virchow.

Fig. 2.



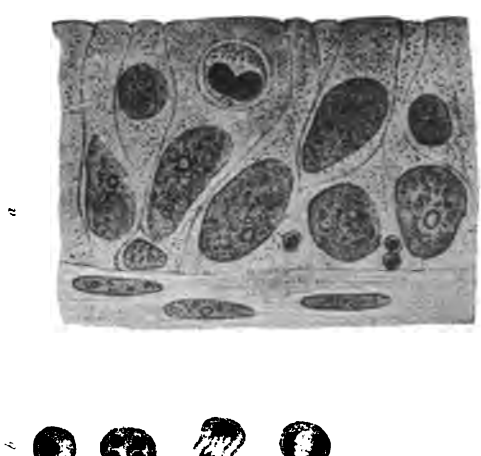
a Plate XII, Fig. 17, after Soudakewitsch.
b Plate VI, Fig. 2, after Soudakewitsch.
c Plate XII, Fig. 7, after Soudakewitsch.

Fig. 3.



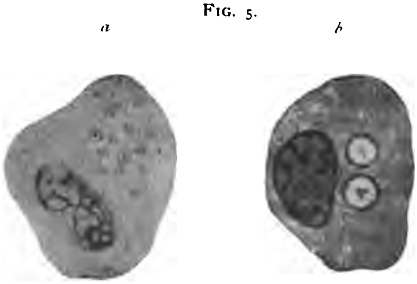
a Plate IV, Fig. 1, after Sjöbring.
b Plate IV, Fig. 14, after Sjöbring.

Fig. 4.



a Adenocarcinoma of the rectum—Thor
b Parasitic forms from above.

Fig. 5.



a Plate II, Fig. 2, after Foa.
b Plate II, Fig. 16, after Foa.

nique employed by these authors was somewhat different from that of others, although based on osmic acid fixation, the stain being safranin and picric acid.

After a most careful review of the forms of inclusions previously described in carcinoma, Borrel[1] concludes that the only bodies which under any circumstances could be considered as parasitic are the typical bird's-eye inclusions. In Figs. 8 and 9, Plate II, Borrel illustrates two large epithelial cells from epithelioma of the maxillary region, containing typical bird's-eye inclusions. (See Fig. 8.) Fig. 9 of this plate likewise shows forms suggestive of nuclear division, to be considered later.

Sawtschenko[2] describes as appearing in several tumors, the origin and number not being given, cell inclusions of the bird's-eye type. Those shown in Figs. 7, 8, 9, 10 and 11 are entirely characteristic. (See Fig. 9.) His preparations were from material hardened in Flemming's solution, stained with safranin.

Ruffer and Walker[3] illustrate these inclusions in Plate XIV, Figs. 4 and 8, from two cases of gastric carcinoma; Plate XVI, Fig. 10, from carcinoma of the breast; Figs. 20, 21, 25, 28, 29, hardened with Flemming and stained with methyl-green, Biondi, also from cancer of the breast.

Ruffer and Plimmer[4] in Figs. 2, 5, 6, 12, 18, 32, 35, 37 and 49 of Plates I, II and III, give excellent illustrations of typical inclusions. (See Fig. 10.)

J. Jackson Clarke[5] illustrates on Plate III, Fig. 6, a group of typical bird's-eye inclusions, and at 7 and 10, masses of what appear to be spore-like bodies of a similar nature. (See Fig. 11.) He considers these inclusions to be sporozoa.

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[1] Borrel.—Evolution cellulaire et parasitisme dans l'epithelioma. *Montpellier,* 1892. *Thêse.*

[2] Sawtschenko.—Ueber schmarotzende Sporozoen in Krebsgeschwülste. *Centralblatt f. Bakteriologie,* Vol. XII, 1892, p. 17.

[3] Ruffer and Walker.—On some parasitic protozoa found in cancerous tumors. *Journal of Pathology and Bacteriology,* 1893, p. 198.

[4] Ruffer and Plimmer.—Further researches on the parasitic protozoa found in cancerous tumors. *Journal of Pathology and Bacteriology,* 1894, p. 3.

[5] J. Jackson Clarke.—Observations on the Histology of cancer. *Centralblatt f. Bakteriologie,* Vol. XVI, 1894, p. 281.

C. H. Cattle[1] describes typical bird's-eye inclusions, and especially calls attention to the fact that the inclusions can be found in the acini of the mammary gland at the margin of cancer of the breast, at the points where the epithelium of the acini is undergoing cancerous transformation. This is probably the first definite reference to the presence of bird's-eye inclusions in the epithelium of the acini, where the epithelium still maintains its typical acinous arrangement. (See Fig. 12.)

Sawtschenko[2] again describes, under a number of cell inclusions of varying forms, certain that represent typical bird's-eye inclusions. Fig. 30, Plate VI (see Fig. 13), carcinoma of the breast, and 32 from the same; Plate V, Fig. 24, the lower figure, from carcinoma ventriculi, and 25, upper figure, carcinoma of the breast, are clearly defined bird's-eye inclusions.

Pianese[3] shows in Fig. 2, Plate IV (see Fig. 14), in one of the cells to the left, well-defined bird's-eye inclusions from carcinoma of the breast.

F. J. Bosc[4] shows in Plate I, Figs. 1, 2, 3, 4, 5, 6, 7, 10, 11 and 38*b*, well-defined bird's-eye inclusions. On Plate II, Fig. 1 (see Fig. 15), are many inclusions of this type. Fig. 2*m*, Fig. 3*x*, Fig. 4*m*, Fig. 1*a*, Fig. 2*m*, Fig. 5*m*, 14, 15, 17 and 18 are from a case of carcinoma of the pancreas and liver; Plate IV, Figs. 26 and 28, epithelioma of the lower lip. On Plate II, Fig. 4 at "mor"; Plate III, Figs. 14, 15, 16, 18 and 19; Plate IV, Fig. 28; Plate V, Fig. 8 at "mor"; Fig. 12 at "mor"; Plate VII, Fig. 2*b* and Plate X, Fig. 4, the author pictures closely arranged groups of these bodies, which he considers to represent spore formation.

H. G. Plimmer[5] in his most recent article describes having found these bodies in a large number of cancers, and gives illustrations

[1] Cattle, C. H.—Observations on the Histology of Carcinomata and the Parasite-like Bodies found in them. *Journal of Pathology and Bacteriology*, Vol. II, p. 367, 1894.

[2] Sawtschenko.—Sporozoen in Geschwülste. *Bibliotheka Medica*, DII, Part 4, 1895.

[3] Pianese. Beitrag zur Histologie und Aetiologie des Carcinoms. *Zeigler's Beiträge*, 1896, Suppl. 1.

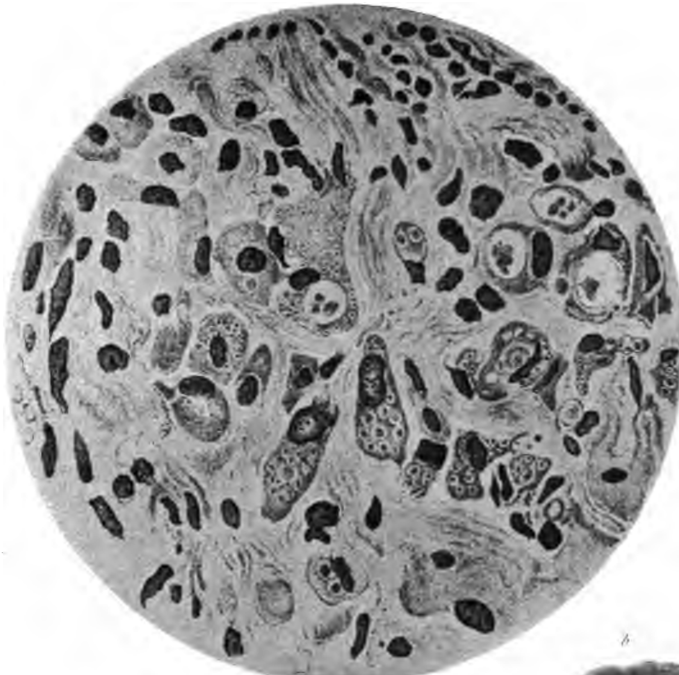
[4] Bosc, F. J.—*A Monograph on Cancer*, Paris, 1898.

[5] Plimmer, H. G.—On the Histology and Etiology of Cancer. The *Practitioner*, April, 1899.

Plate XIX.

Fig. 6.

a



b

a Plate XII, Fig. 3, after Kürsteiner.
b Plate XII, Fig. 6, after Kürsteiner.

Fig. 7.

Plate VII, Fig. 2, after Podwyssozki and Sawtschenko.

Fig. 8.

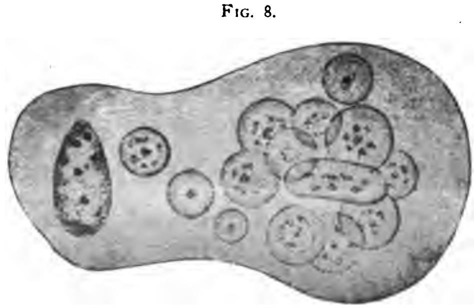
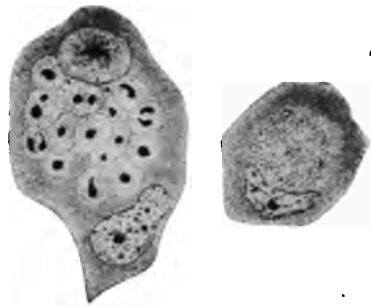


Plate II, Fig. 9, after Borrel.

Plate XX.

Fig. 9.

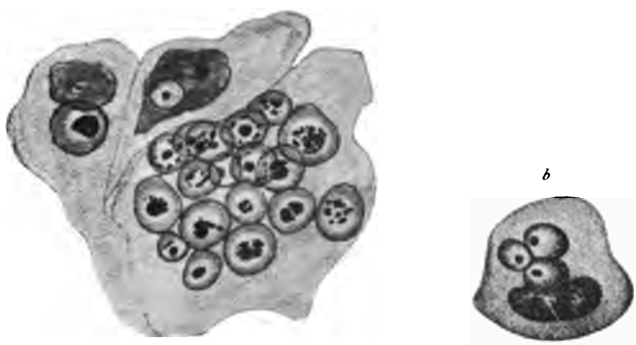
a *b*



a Plate I, Fig. 10, after Sawtschenko.
b Plate I, Fig. 9, after Sawtschenko.

Fig. 10.

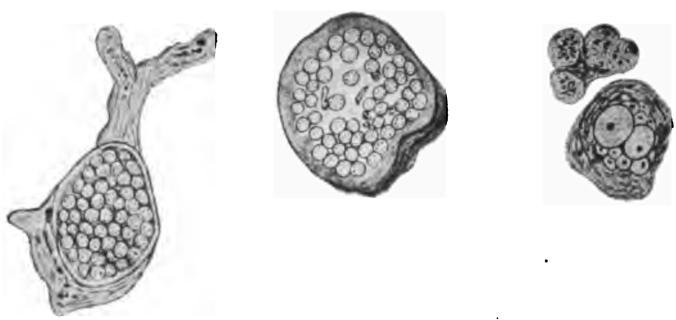
a *b*



a Plate I, Fig. 5, after Ruffer and Plimmer.
b Plate XXIII, Fig. 11, after Ruffer and Plimmer.

Fig. 11

a *b* *c*



a Plate III, Fig. 10, after J. Jackson Clarke.
b Plate III, Fig. 7, after J. Jackson Clarke.
c Plate III, Fig. 6, after J. Jackson Clarke.

from a cancer of the breast which contained unusual numbers. The figures on Plate I (see Fig. 16), Figs. 7, 8, 9, 10 of Plate II illustrate these inclusions.

Sjöbring[1] in his most recent publication, illustrates typical cell inclusions of especial interest. These are illustrated as appearing (see Fig. 17) in the epithelial cells of the epididymis of a rabbit, from the immediate neighborhood of a fragment of carcinoma which had been transplanted under sterile conditions into the tunica vaginalis of the animal.

E. von Leyden,[2] in Plate I, illustrates inclusions from a carcinomatous lymph node from carcinoma of mamma and a carcinoma of the cecum. He suggested the term "bird's-eye inclusion" which aptly describes the appearance of these structures.

Gaylord[3] illustrates these bodies in Plates VIII, IX, XIV and Figs. 2 and 3, Plate XV; Figs. 1, 2, 3, and 4, Plate XVI, all taken from carcinoma of the breast.

Feinberg[4] describes characteristic bird's-eye inclusions embedded in the protoplasm of cancer cells, as well as a form which he believes to be extra-cellular, which appears to be without a central body. His article is unaccompanied by illustrations but from examination of his specimens there is no doubt Feinberg in part deals with the typical inclusions.

Greenough[5] illustrates on Plate XXXIII, Figs. 2 and 3, what appear to be typical bird's-eye inclusions. Plate XXXV, Fig. 3, appears to contain a typical inclusion. Those shown on Plate XXXIII were from a cyst adenoma of the breast. Fig. 3, Plate XXXV, is from carcinoma of the breast.

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[1] Sjöbring, N.—Ueber die Microörganismen in den Geschwülsten. *Centralblatt f. Bakteriologie,* Vol. XXVII, 1900.

[2] Von Leyden, E.—Zur Ætiologie des Carcinoms. *Zeitschrift für klin. Medecin,* Berlin, 1901.

[3] Gaylord, H. R.—The Protozoön of Cancer. *American Journal of the Medical Sciences,* May, 1901.

[4] Feinberg.—Zur Lehre des Gewebes und der Ursache der Krebsgeschwülste. *Deutsche med. Wochenschrift,* XXVIII, 11, p. 185, 1902.

[5] Greenough.—Cell Inclusions in Cancer. *Journal of Medical Research,* Vol. VII, No. 2.

Nösske[1] illustrates on Figs. 1, 2, 3 4*c* and 10, typical bird's-eye inclusions.

E. von Leyden[2] illustrates on Plate I (see Fig. 18) cells containing these inclusions from a case of pulmonary carcinoma and cancer of the breast. In Fig. 4*a* and *d* he shows a cell containing large masses of these inclusions, which he thinks are the termination of a process of spore formation. Figs. 3*a* and 3*b* show the same accumulation of closely packed smaller bodies in another cell. Several of his illustrations represent the bodies in the fresh state stained and unstained.

Posner[3] has recently published five drawings made by himself in 1876 while a student of Wagner's. (See Fig. 19.) These represent characteristic bird's-eye inclusions from carcinoma of the breast and one illustration of characteristic bird's-eye inclusions in a sarcoma cell from sarcoma of the spinal cord. This is the first recorded observation of bird's-eye inclusions in sarcoma.

Klimenko,[4] in an article reviewing a previous article of Feinberg, describes bird's-eye inclusions which he thinks, however, are not identical with those described by Feinberg. He was unable to find an inclusion corresponding exactly to those given by Feinberg. He has attempted to determine by microchemic reactions whether the bird's-eye inclusions are the result of degenerative processes, and concludes that they give no micro-chemical results indicating that thev are. He agrees with Nösske that the inclusions are probably the result of secretive and excretive activity, or perhaps even evidence of reserve food stuff (glycogen) in the cells. He observed the fact that in certain cases of carcinoma of the breast, where there was great metotic activity in the cells, but few inclusions were present. On the other hand, in certain carcinomata, in which proliferation was not markedly active, a large number of inclusions could be found. He was unable to determine a direct relation between the presence of

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[1] Nösske.—Untersuchungen über die als Parasiten gedeuteten Zelleinschlüsse im Carcinom. *Deutsche Zeitschrift für Chirurgie,* Bd. LXIV.

[2] Von Leyden, E.—*Ueber die Parasiten des Krebses,* 1902.

[3] Posner.—Notiz über vogelaugenänliche Einschlüsse in Geschwülstzellen. *Archiv. für klin. Chirurgie,* Bd. LXVIII, Heft 3.

[4] Klimenko.—Eine Nachprüfung der Arbeit Dr. Feinberg's über seine Krebsparasiten. Beitrag zur Frage über die Einschlüsse in und zwischen den Krebszellen. *Centralblatt für Pathologie,* Vol. XIII, No. 21, p. 837.

Plate XXI.

Fig. 12.

Plate XXII, Fig. 9, after Cattle.

Fig. 13.

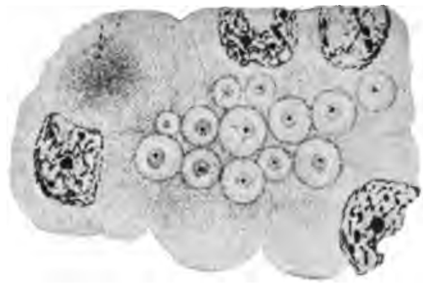


Plate VI, Fig. 30, after Sawtschenko.

Fig. 14.

Plate IV, Fig. 2, after Pianese.

Fig. 15.

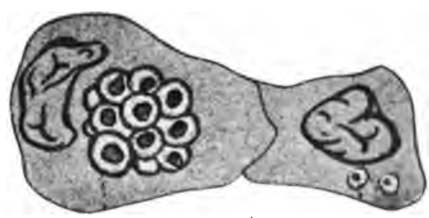
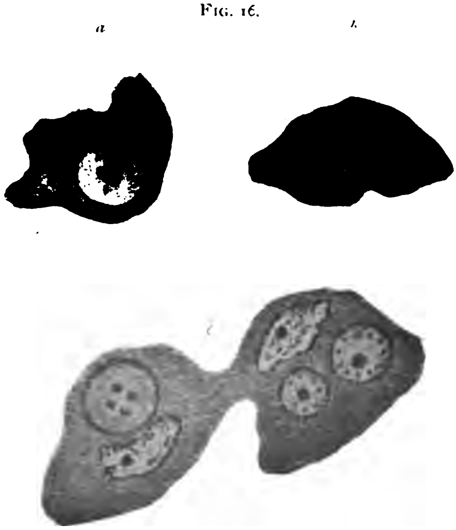


Plate II, Fig. 4, after Bosc.

Fig. 16.



a Plate I, Fig. 5, after Plimmer.
b Plate I, Fig. 6, after Plimmer.
c Plate II, Fig. 9-10, after Plimmer.

Fig. 17.

Fig. 1, after Sjöbring.

inclusions and metotic activity in the neighboring cells. He was never able to detect inclusions in cells undergoing division.

The theories advanced as to the significance of these bodies: (*a*) as degenerations of various kinds of the cytoplasm and nuclei of the cells. Of the authors already cited those who have undoubtedly observed and illustrated the inclusions which we are considering, Virchow, Pianese, Greenough and Nösske, interpreted them as the result of transformation or degenerations of the component part of the cells. Virchow in his first article interpreted these bodies as metamorphosed nuclei. In his second article he advanced the theory of endogenous cell formation and believed that the inclusions illustrated were cells thus formed. Borrel[1], who previously held that these bodies were of a parasitic nature, has recently suggested that they are produced by alterations in the centrosomes of the cancer cells. Pianese's article deals with a great variety of inclusions and only those quoted, Fig. 2, Plate IV, can be accepted as sufficiently characteristic to be included under the type we are considering. Pianese's investigations led him to the conclusion that all the structures illustrated were the result of different forms of metamorphosis, vacuolisation of the protoplasm, and hyaline and colloid degeneration. It would appear from the recent publication of Pianese that he has somewhat modified his interpretation of at least certain varieties of the inclusions described in his extensive monograph. In his most recent[2] article, which deals with a protozoon infecting the renal epithelium of the guinea-pig, Pianese concludes that the presence of this organism leads to the development of active mitotic changes of the adjacent epithelial cells. These figures are either typical or atypical, and the latter closely resemble the forms of mitosis found in carcinoma. He likewise finds that the epithelium presents other characteristics (karyolysis, karyorrhexis, nucleorrhexis and nucleolysis) uniformly observed in cancer cells. Lastly, he finds that many of the epithelial cells contain inclusions closely resembling certain

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[1] Borrel.—Les Theories parasitaires du cancer. *Ann. de l'Institut Pasteur*, Vol. XV, 1901.

[2] Pianese.—Ueber ein Protozoon des Meerschweinchens. *Zeitschr. f. Hygiene und Infectionskrankheiten*, Vol. XXXVI, Part 3.

varieties found in carcinoma. He was unable to satisfy himself as to whether these inclusions were stages in the development of the parasite or changes produced in the cell by the indirect action of the organism. It would appear from this article that Pianese does not at present hold fast to the conclusion, that all the cell inclusions in cancer are the result of degeneration of the cells.

Greenough concludes these bodies are the result of secretory activity of the cell. He bases his conclusions on the facts that the inclusions are not found in epithelioma or sarcoma, and that they are found in non-cancerous diseases of the mammary gland, *i. e.*, fibroadenoma. Nösske arrives at a conclusion similar to that of Greenough, believing the inclusions to be the result of secretory activity on the part of the cells. Borrel[1] interprets many of the cell inclusions as centrosomes.

Besides these authors a number of critical articles have appeared. Lubarsch[2] believes that the inclusions may be one of the four following: First, they may be the result of vacuolisation of the cell protoplasm in which protoplasmic remains become condensed and form a central body. Second, they may be centrosomes (Borrel), numbers of which have been found in giant cells by Heidenhain and Benda. Third, the bodies are the result of the phagocytic activity of the cancer cells which take up red blood corpuscles, these disintegrate, the remains forming the central body. Fourth, the bodies are caused by secretion granula around which a halo of pale protoplasm is formed. To these four may be added two more. Fifth, the belief that they are the result of special secretory activity on the part of the cells (Greenough, Nösske); and, sixth, Hansemann[3] believes that these bodies are formed as a result of the fixative which extracts the water from hyaline material embedded in the protoplasm. As a result of this extraction of water the hyaline material remains as a condensed central mass which forms the central body.

It will be seen from the above enumeration, that investigators who have interpreted these so characteristic inclusions as the result of

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[1] Loc. cit.

[2] Lubarsch.—*Pathologische Anatomie und Krebsforschung*, 1902.

[3] Hansemann.—Die mikroskopische Diagnose der bösartigen Geschwülste. Second Ed., 1902, Berlin.

metamorphosis of the cytoplasm, are in no way agreed as to the manner in which they are formed. Those who hold that the bodies are probably parasitic in their nature, have advanced certain arguments in objection to the above interpretation.

First of all, all investigators who have interpreted the bodies as parasites have failed to find characteristic inclusions in any other structures than tumors. It is claimed that in properly fixed sections the bodies present a characteristic appearance, and can be distinguished from simple vacuolisation of protoplasm. The most recent utterance on this subject is that of Benda.[1] He states that although he has searched carefully for these inclusions in all kinds of tissue he has failed to find them in anything but malignant growth. It must appear, then, that if the bodies are the result of vacuolisation of protoplasm, this form of degeneration is characteristic of carcinoma cells. An apparent exception to this statement is that contained in the publication of Nösske. This author claims to have found typical bird's-eye inclusions in the epithelium of the normal acini of the breast. An analysis of this statement shows first, that the normal breast referred to was located at the margin of a nodule of carcinoma. Through the courtesy of Prof. Marchand, the writer has had the privilege of seeing this section. After carefully viewing the preparation it appeared to us that the epithelium in question had already begun to proliferate. In one portion of the acinus there were three distinct layers of the epithelium. We were of the opinion in this case that the epithelium had already undergone cancerous metamorphosis. Dr. Nösske exhibited this preparation at the 31st Surgical Congress in Berlin, April 3, 1902. It was viewed by a number of pathologists, a majority of whom were likewise of the opinion that the epithelium had already undergone carcinomatous transformation. The presence of the inclusions, therefore, at the margin of carcinoma nodules would rather more strongly indicate that they were of parasitic nature than that they were degenerations. The observation is not new, the distribution of the inclusions in the acini at the margin of carcinoma of the breast having been referred to and accurately described by Cattle.

[1] Benda.—Sitzung der Karzinom Comite, Oct. 4, 1902.

The bodies illustrated by Greenough found in fibroadenoma of the breast are undoubtedly characteristic bird's-eye inclusions, but inasmuch as fibroadenomata are known in many cases to become transformed into cancer, and as the etiology of this form of tissue development is unknown, their appearance in this class of tumor in no way excludes the possibility of their being parasites. The inclusions shown by Nösske, as appearing in the bronchial epithelium in a case of congenital syphilitic pneumonia in a new-born child, are so essentially different from the bird's-eye inclusions as to be excluded, even from the illustrations which accompany his article.

As to the second possibility that the bodies are centrosomes, as noted by Benda and Heidenhain (Borrel and LeCount[1]), this supposition is rendered improbable by the great number occasionally found in a single cell. Kürsteiner counted as many as 80 in one cell, and Plimmer[2] illustrates a cell containing 27 inclusions. Fig. 23 illustrates a cell in which 18 cell inclusions can be counted.) Secondly, the fact that centrosomes can be found in cells containing these inclusions and can be definitely distinguished from them should dispose of this interpretation of the body.

In this connection, the evidence of Benda (*Verhandlungen der deutschen Gesellschaft für Chirurgie,* 31st Surgical Congress, Berlin, April 3, 1903, p. 73,) is of great importance. One of the first to describe centrosomes, and quoted by Lubarsch as an authority, he states first that centrosomes have often been sought for in carcinoma cells without their presenting any pathological alterations. He states that he has recently, with new and specially proved methods, investigated this question, and holds that the *theory of Borrel is incorrect,* in that he has repeatedly found the centrosomes intact in cells which contained numbers of the bird's-eye inclusions. He holds that the hope of explaining the abnormal proliferation of carcinoma cells as the result of alterations of the centrosome is fruitless.

Third, the interpretation of these bodies as disingtegrating red blood cells taken up by the epithelium (Lubarsch) has been advanced

[1] *Journal of Med. Research.*

[2] Loc. cit.

by various observers. This criticism has likewise been applied to preparations of our own in which we had injected Plasmodiophora spores into the tissue of warm-blooded animals, in repeating the experiments of Podwyssozki[1] where Plasmodiophora spores were taken up by the phagocytic connective tissue cells of the animal and presented an appearance, in may cases, indistinguishable from the bird's-eye inclusions in carcinoma. In attempting to definitely exclude the red blood cells as a factor in the production of these forms, which we held to be metamorphosed spores, we examined a number of specimens taken from nodules developing on the peritoneal surface of frogs which had been inoculated in the same way. These nodules were composed of endothelial cells (as described by Podwyssozki) containing the spores of Plasmodiophora Brassicæ, many of which again presented an appearance identical with the cell inclusions in carcinoma, and identical with the spores embedded in the connective tissue phagocytes surrounding the fragments of implanted clubroot in warm-blooded animals. (See Fig. 23.)

The results of these two lines of experimentation were exactly the same, but the great difference in the red blood corpuscles of the warm-blooded and cold-blooded animals, in the first case non-nucleated, in the second case much larger and nucleated, left no doubt that the inclusions in both cases were the metamorphosed spores of Plasmodiophora Brassicæ. In neither series of experiments were we able to determine that the phagocytes had taken up red blood cells, although in other pathological conditions, *i. e.*, typhoid fever, it is a recognized fact that phagocytic cells commonly take up the erythrocytes. The difficulty of determining the origin of inclusions in cells without the aid of experimentation is emphasized in this case. Many of these bodies are larger than red blood corpuscles, and in properly prepared specimens we have never been able to find any ground for holding that they were altered erythrocytes. The fact that in many cases the central bodies of the bird's-eye inclusions can

[1] Podwyssozki.—Myxomyceten, resp. Plasmodiophora Brassicæ Woron. als Erzeuger der Geschwülste bei Tieren. *Centralblatt für Bakteriologie*, Vol. XXVII, p. 97.

be stained with a nuclear stain, likewise speaks against this supposition.

Fourth and fifth, that the bodies are not secretion granula or the result of special secretory activity on the part of the cell is more difficult to prove, but the fact that they have occasionally been found (Posner) in sarcomata render either explanation rather improbable. The statement of Nösske that they are only found in glandular epithelium and almost exclusively in the mammary gland, a view which Greenough holds, and to which we were previously inclined ourselves, is shown to be incorrect by a critical review of the literature of the earlier writers. This shows that undoubted birds's-eye inclusions have been found in carcinoma arising from other types of epithelium.

Sixth, that the characteristic appearance of these bodies is not due to any action of the hardening process (Hansemann) is shown by their *constant appearance in fresh material, where they have later been found in hardened and stained sections.*

As parasites.—With the exception of the authors above mentioned, the remainder of those who have accurately described or illustrated these inclusions have interpreted them as parasites. The earlier investigators compared them to recognized types of protozoa, notably the coccidia and the gregarinæ. Many of these authors describe, besides the forms which we are considering, larger and more complex structures presenting appearances not unlike certain forms in the development of these organisms. The younger form of coccidium perforans (Leuch) (coccidium oviforme), in the epithelium of the intestinal tract of rabbits is extremely like in appearance the bird's-eye inclusions of cancer.[1] The readiness with which ectogenous form of coccidia can be detected in the tissues of the animals infected, has, however, weakened the force of this comparison, because of the absence in the fresh material of cancer of forms presenting anything like the definite characteristics of the ectogenous cycle of the coccidia. A class of organisms which has attracted the attention of the more recent writers on the subject is the mycetozoa, especially one of the

[1] See Fig. 221, Lang, Lehrbuch der vergleichende Anatomie der wirbellosen Thiere. Zweite Lieferung. Protozoa.

group, Plasmodiophora Brassicæ, an organism which causes tumors and outgrowths in plants. This class was previously placed among the lower types of fungi, but more recently has been accepted as a variety of protoza, Doflein, in his recent book on the subject classifying it under the rhizopoda.

The first to call attention to a possible connection between cancer and kohlhernia was R. Behla. He noted the prevalence of this disease in plants in localities in which cancer was prevalent. He inoculated animals with fragments of the plant tumors and noted that granulation tumors resulted. He did not, however, detect the presence of the parasite in the tissue cells. Podwyssozki[1] after viewing the preparations of Nawaschin in a preliminary announcement, called attention to the fact that certain forms of this organism and certain inclusions in cancer presented great points of similarity. He afterward reported experiments upon rabbits, guinea-pigs, frogs and axolotls, in which he had succeeded in producing infection and had detected the presence of the spores in the cells of the infected animal. He found that the introduction of the spores of plasmodiophora in the tissues of both cold and warm-blooded animals, led to the development of tumors of considerable size made up of cells derived, either from the connective tissue, or from the endothelium of the surrounding lymph spaces. In the latter case the tumors presented the characteristics of an endothelioma. He was able to determine that the presence of the parasite led to the proliferation of the nuclei of the infected cells.

Following Podwyssozki, von Leyden[2] likewise noted the similarity between bird's-eye inclusions and the amœboid form of Plasmodiophora in the plant cell. Feinberg[3] emphasises the same similarity. Nösske does not think the similarity of the cell inclusions and the amœboid form of Plasmodiophora to be so great.

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[1] Loc. cit.

[2] von Leyden, E.—Zur Ætiologie des Carcinoms. *Zeitschr. f. klin. Medecin*, Vol. XLIII, Part ½. Ueber die Parasiten des Krebses. *II Ergänzungsband vom klinischen Jahrbuch.*

[3] Feinberg.—Ueber den Erreger der krankhaften Auswüchse des Kohls (Plasmodiophora Brassicæ Woronin). *Deutsche med. Wochenschr.*, March 3, 1902.

All these comparisons, except that of Behla are based upon the publication of S. Nawaschin.[1] Upon receipt of this article we were greatly surprised at the remarkable similarity between many of Nawaschin's figures and bird's-eye inclusions in cancer. According to Nawaschin, the organism first appears in the plant in the form of an amœba, after having entered as a swarmer. These amœbæ are found in the plant cells lying in the sap spaces and, except in very early infections, a number were found in each cell. The amœbæ contain in their protoplasm when observed in the fresh state, highly refractive granules of equal size, which present an appearance very much like fat. The nuclei are spherical or oval and consist of a vacuolous structure with a central body. It is this nucleus which so resembles the bird's-eye inclusions. The organism having become transformed into an amœba in the plant cell, *lives a strictly symbiotic existence with the infected cell.* It divides by a special form of cell division which we shall consider in detail, and only when the plant cell is exhausted is the cycle inaugurated, which leads to spore formation.

This latter cycle, that of spore formation, is entirely distinct from the process of nuclear division by which the amœbæ increase in number. In the younger forms of the organism (Fig. 20), the protoplasm surrounding the nucleus of the parasite is scarcely distinguishable from the protoplasm of the plant cell and extends into it in delicate prolongations. The change leading to nuclear division in the amœba, are first found in the appearance of fine grains of chromation within the nucleus, scattered indiscriminately in the clear space between the central body and the periphery. (Fig. 21*a.*) The nuclei in this stage are somewhat larger than immediately after division. These chromatin granules group themselves about the central body which first becomes indistinct (Fig. 21*b*), and then divides. They are more or less definitely arranged in the form of a circle in the plane of the division. (Fig. 21*c.*) A section through the nucleus in this stage shows the two central bodies closely approximated, with the smaller chromatin granules in the transverse axis.

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[1] Nawaschin, S.—Beobachtungen über den feineren Bau und Umwandlungen von Plasmodiophora Brassicæ Woron. im Laufe ihres intracellularen Lebens. *Flora,* 1899, Vol. LXXXVI, Part 5.

A section in the transverse axis shows the central body surrounded by a ring of chromatin granules, presenting the appearance of a rosette. (Fig. 21*d*.) The nucleus in this stage has already assumed an oval form and the central bodies then withdraw to the poles of the cell. (Fig. 21*e*.) In this stage they are sometimes connected by one or two threads of chromatin which later disappear. Division is then completed by the capsule folding in at the center, leaving two perfectly formed nuclei each with a central body, the two closely approximated. (Fig. 21*f*.) In this way a single amœba may possess a number of nuclei.

Aside from the characteristic nucleus, the protoplasm of the amœba is of interest, containing, as it does, in the fresh state, coarse granules of uniform size. These granules are blackened by osmic acid and on the extraction of the fat from the preparations they disappear, leaving a coarsely reticulated protoplasm. (Fig. 21*f*.) The central body of the nucleus, when stained with Flemming's triple stain, reacts variably to the stain. When in the amœboid form the central body of the nucleus stains brilliant red. In the first stage of spore formation, the central body stains a deep blue-black. This point is of importance inasmuch as certain discrepancies in the staining of the central bodies of the bird's-eye inclusions have been previously noted.

The process which leads to spore formation is entirely distinct from that by which the amœba, as such divides. In preparation for this process the nuclei of the amœba divides repeatedly by the method already described, thus each amœba contains a number of small nuclei. The margins of the amœba then become indistinct, the nuclei likewise become less distinct and the different amœbæ coalesce. The central body of the nucleus then becomes very indistinct, the protoplasm granular. The nuclei at this stage contain fine granules and are with difficulty distinguished from the surrounding protoplasm. The whole structure now forms a plasmodial mass. There now develops in each nucleus a well-defined spindle with medullary plate, all of the nuclei dividing at once. This process of division follows the recognized types of mitosis and when complete the entire mass breaks down into small amœbæ, each containing one

nucleus. These are at first of irregular shape and stain poorly. The irregularly shaped myxamœbæ are gradually rounded and condensed until they ultimately form spherical bodies of similar size with well-defined margins, each containing a highly refractive central body. It is to be noted that *the complete spore again presents an appearance not unlike the nuclei of the amœbæ.*

Recognizing the great similarity between the bird's-eye inclusion in cancer cells and the nuclei of the amœba in Plasmodiophora in the plant cell, a similarity which to a lesser degree is shared by spores of Plasmodiophora, it occurred to us to search our preparations for evidence of some form of division in the inclusions, and likewise to determine if the protoplasm surrounding the inclusions could be distinguished from the remaining protoplasm of the epithelial cell. In searching our preparations we came upon one which has already served us for photography, the illustrations of which appear in our previous publication, being the low power illustrations on Plate VIII, Plate XIV, Fig. 1, Plate XVI.[1]

This preparation consisted of a thin section, approximately 2 mm. square, taken from the margin of a rapidly growing carcinoma of the breast. It contained a large number of inclusions, in many fields every cell containing one or more. The fixation of this preparation was unusually successful and the differentiation excellent. We had little difficulty in repeatedly finding forms extremely suggestive of the method of division, illustrated in Fig. 21—*a, c, d, e* and *f* from Nawaschin. Fig. 24 was repeatedly found and appears to represent a stage similar to that shown in Fig. 21*a* Nawaschin. We next repeatedly encountered inclusions in which the central body had divided and in nearly every case found two small granules of chromatic material in the transverse axis so arranged as to present an appearance exactly like Fig. 21*e* from Nawaschin. In Fig. 25 an inclusion presenting this appearance is shown. The two granules in the transverse axis are extremely small and were photographed with difficulty. It is this form which, when sectioned in the transverse axis, produces the rosette appearance which was likewise repeatedly encountered. In Fig. 26 the central body lies

[1] *American Journal Med. Sciences.*

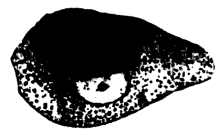
Plate XXII.

Fig. 18.

Plate I, Fig. 4*a*, after von Leyden.

Fig. 19.

a



b

a Fig. 3, after Posner.
b Fig. 5, after Posner.

Fig. 20.

Plate XX, Fig. 6, after Nawaschin.

Fig. 21.

a *b* *c* *d* *e* *f*

a Plate XX, Fig. 14, after Nawaschin.
b Plate XX, Fig. 17*f*, after Nawaschin.
c Plate XX, Fig. 17*e*, after Nawaschin.
d Plate XX, Fig. 17*d*, after Nawaschin.
e Plate XX, Fig. 18*d*, after Nawaschin.
f Plate XX, Fig. 15, after Nawaschin.

somewhat below the plane of focus and the rosette appearance is not so characteristic as occasionally seen. Many forms were found in which the rosette was apparently sectioned in an oblique plane so that but one half of the rosette appeared in the inclusion. Fig. 27 shows what appears to be the next stage in the process of division, the two central bodies having withdrawn to the poles of the cell, and separation of the two by the capsule is suggested by the appearance of the inclusion. Bodies which had apparently divided were repeatedly found, Fig. 28 representing this stage. In Fig. 29 are likewise seen bodies cut somewhat obliquely, also representing this stage. We had no difficulty in finding all of these forms repeatedly.

A careful examination of the protoplasm surrounding the inclusions was made to determine whether a differentiation of the possible protoplasm of the parasite and that of the epithelial cell could be made. In many cases a distinct reticulation of the protoplasm was visible as in that surrounding the two inclusions in Fig. 28. In one or two portions of the section we found what appeared to be inclusions surrounded by reticulated protoplasm which had become detached from the nuclei of the cells in which they were included. Fig. 29 shows an inclusion of this sort surrounded by reticulated protoplasm, which has become detached from the nucleus of the cell lying slightly to the left. In certain cells we found large numbers of small inclusions closely packed. In these we were unable to find any evidence of the changes above described. Fig. 23 shows a cell containing a number of bodies somewhat more distinct than those containing the apparent nuclear changes.

A number of observers have undoubtedly spoken of similar groups of inclusions, as representing spore formation. (Bosc, von Leyden, Jackson Clarke.) The similarity of inclusions of the type shown in Fig. 23 to those already described, led us to repeat the experiments of Podwyssozki, for the purpose of ascertaining what appearance the spores of Plasmodiophora Brassicæ presented when embedded in the connective tissue and phagocytic cells of animals. This series of experiments was undertaken with uniform results. The spores could be found in the large connective tissue phagocytes embedded in the protoplasm of the cells. They consisted for the

greater part of spherical bodies of vacuole-like appearance with a central body. Hardened and stained with Plimmer's method, they stained, as does the protoplasm, and presented an appearance in size, form and other characteristics indistinguishable from the cell inclusions in cancer. Fig. 22 represents two large phagocytic cells from the margin of an implanted fragment of clubroot in a guinea-pig, removed after nineteen days. The cell to the left contains a form of inclusion most commonly seen. Between the two cells are two larger forms which are constantly encountered in the fresh scrapings. These are spherical bodies with delicately defined limiting membranes and with fine granular contents or in some cases filled with homogeneous material. The two bodies shown lying directly between phagocytes are undoubtedly of this nature. It is probable that they represent a stage in degeneration of the spores. They are of interest inasmuch as bird's-eye inclusions in cancer are commonly encountered, which contain finely granular material and have invariably been quoted in support of the degeneration theory. It is evident that these spores under certain conditions undergo degeneration, which would render their differentiation from other products of degeneration difficult. Nösske has recently advanced a line of reasoning of this nature to show that all the bird's-eye inclusions represent a form of secretory activity on the part of the cells. Those who have studied the bird's-eye inclusions have apparently failed to consider the possibility of the inclusions, if of parasitic origin, undergoing a process of degeneration.

It will be seen from the foregoing that in the spores of Plasmodiophora Brassicæ, we have a form of parasite which, embedded in the protoplasm of a cell, frequently presents an appearance indistinguishable from certain of the cell inclusions in cancer. It must, therefore, be conceded that the inclusions in cancer which so *closely resemble them are possibly of parasitic origin. Furthermore, the detection in the inclusions in a single slide, of a cycle of changes so closely representing the process of nuclear division in the amœboid form of Plasmodiophora, must be viewed as strongly indicating the parasitic nature of these inclusions.*

Some of the phases of what we view as a process of nuclear division in the bird's-eye inclusions are indicated in the illustrations ac-

companying the articles of Soudakewitsch, Borrel and Plimmer. Fig. 2, *b*, which is Fig. 2, Plate VI, from Soudakewitsch, shows a body to the left and above which corresponds with Fig. 3 of the text from Nawaschin. Fig. 2, *c*, which is Fig. 7, Plate XII, from Soudakewitsch, represents a group of bodies nearly all of which present typical rosette forms. Fig. 2, *a*, which is Fig. 17, Plate XII from Soudakewitsch shows a body to the left with two central bodies apparently in the act of dividing. Fig. 8, from Borrel, shows a large epithelial cell containing a number of inclusions, some with single central bodies, but a majority showing typical rosette forms. Fig. 16, *a*, from Plimmer (loc. cit.) shows an inclusion with central body surrounded by a number of grains of chromatin. Fig. 16, *b*, from Plimmer, shows a typical rosette form and Fig. 16, *c*, from Plimmer, shows three inclusions, two of typical rosette form and one with four bodies arranged in a manner not unlike Fig. 4, from Nawaschin. Under the head of Methods of Division, Plimmer (loc. cit.) states that the division into two is by far the most usual method of multiplication. This is effected, he believes, by a form of budding, or the nucleus becomes somewhat oval in shape and then divides into two parts. These soon become equal and separate, and then the capsule throws in septa from either side between the divided nucleus, which meet. They then separate from each other and become two separate individuals. The rosette form Plimmer interpreted as evidence of a form of division in which portions of the nucleus have become detached and arranged at the circumference of the organism. This he believes was followed by a process of segmentation with the formation of a number of parasites. With reference to the statement made by Plimmer that these bodies divide by a form of budding, we have never been able to detect any appearance confirming this observation. We are of the opinion that the rosette form corresponds closely to that described by Nawaschin and shown in Fig. 5 of the text.

Conclusions.—In summing up we would conclude that the spores of Plasmodiophora Brassicæ in the phagocytic cells of both warm and cold-blooded animals, when fixed and stained with the methods employed in the investigation of bird's-eye inclusions in cancer, under certain conditions, present an appearance indistinguishable

from these inclusions. Second, that a series of changes can be found in the bird's-eye inclusions in cancer closely resembling the process of nuclear division, as described by Nawaschin in the amœboid form of Plasmodiophora Brassicæ.[1]

DESCRIPTION OF PLATE XXIII

Fig. 22. Large phagocytic cells from guinea-pig, found at margin of implanted clubroot nineteen days after implantation. At *a* Plasmodiophora spore embedded in protoplasm of cell. Central body of spore eccentrically placed. No condensation of cell protoplasm surrounding spore. At *b* two larger forms of spores containing protoplasmic masses (possibly partly developed swarmers).

Figs. 23 to 29 are taken from one slide, carcinoma of the breast, hardened and stained with Plimmer's method. Magnification of all figures, 22 to 29 × 940.

Fig. 23. Epithelial cell from carcinoma of the breast, containing 14 round cell inclusions of like size and appearance. Same magnification as Fig. 22. (Compare with *a*.)

Fig. 24. Cancer cells, containing large inclusions with well developed central bodies. Scattered between central body and periphery of inclusions numbers of chromatin granules. (Compare with first stage of division of intracellular amœba of Plasmodiophora as shown by Nawaschin.)

Fig. 25. Elongated cell inclusion with two central bodies closely approximated. In the transverse axis two smaller grains of chromatin. (Compare with Fig. 2 from Nawaschin.)

Fig. 26. Cross section of inclusion similar to that shown in Fig. 25. The central body lies just below the focal plane, the grains of chromatin arranged in the form of a rosette about it. (Compare with Fig. 3 from Nawaschin.)

Fig. 27. Oval inclusion with two central bodies widely separated at poles. Suggestion of division with two bodies barely visible. (Compare Fig. 4, Nawaschin.)

Fig. 28. Two inclusions immediately after division. Central bodies well defined. Inclusions surrounded by reticulated protoplasm.

Fig. 29. Group of cells containing inclusions. At *a* an inclusion surrounded by reticulated protoplasm has become detached from the cell in which it was embedded. The inclusion in the surrounding reticulated protoplasm presents an appearance extremely like the myxamœbæ of Plasmodiophora.

February 1, 1903.

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[1] On the point of sending this article to press, we have received a short epitome in the *Deutsche Medizinal-Zeitung*, Beilag für Karzinomlitteratur, of an article by S. Prowazek, entitled "Zur Kernteilung der Plasmodiophora Brassicæ Woronin." It is impossible to judge from the epitome to exactly what conclusions the author has arrived, but it would appear that he has questioned the significance of the changes described by Nawaschin.

Plate XXIII.

Fig. 22.

Fig. 23.

Fig. 24.

Fig. 25.

Fig. 26.

Fig. 27.

Fig. 28.

Fig. 29.

SUGGESTIONS FOR THE BIOLOGICAL STUDY OF CANCER.

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It will be unnecessary for me to review in these pages the two sides of the controversy relating to Protozoa as causing certain human diseases. The historical aspect of the cancer problem in this connection has been ably handled by Dr. Park and Dr. Gaylord and needs no *a priori* defense from the biological side. Dr. Gaylord and others are wont to regard the " vaccine bodies " in Vaccinia and in Variola and the cellular inclusions in Carcinoma as similar in nature, and the position which has been taken in this Laboratory in regard to the biological significance of these inclusions is well known. Thanks to the discoveries of Dr. Councilman we now know that the " vaccine bodies " form one phase of the life-history of the protozoan organism which causes smallpox, while other stages, found only in Variola, penetrate the nucleus and give rise to cell inclusions of a very different type. It has been my privilege to work out the entire life-cycle of the smallpox organism upon material provided by Dr. Councilman, and the question as to the specific organism of smallpox is no longer open to doubt. Many of the other diseases belonging to the same group as smallpox (the exanthemata) will in all probability be shown to have a like etiology.

The fact that the cause of a malignant disease like smallpox, which has baffled scientific research for so many years, can be traced directly to a protozoon having a definite systematic position must strengthen the contention made for a like origin of cancer. Notwithstanding the wide difference in the clinical aspects of the two diseases, this is particularly so when we consider the striking

similarity existing between the " vaccine bodies " and some forms of the cell inclusions of cancer. Such a contention should be made, however, only as a working hypothesis, and until material is obtained which will demonstrate without doubt that the inclusions in Carcinoma are phases of an organism the advocates of this hypothesis should be content to work upon the possibility alone.

It would be very difficult at the outset to plan out a series of conclusive experiments demonstrating the presence and activity of a specific micro-organism as the cause of Carcinoma. The chance of hitting upon a successful experiment would be extremely slight, and the possibility of finding an ectogenous phase of such an organism would be small indeed. To my mind it would be far more profitable scientifically to work out in clear detail some well-known growth due to a specific protozoon, such, for example, as the study suggested by Dr. Gaylord of the tumorous outgrowths in some vegetables which are known to be due to the specific organism *Plasmodiophora brassicæ*. In the second place, inclusions in carcinomatous tissues should be studied by specialists trained to the study of Protozoa and not left exclusively to pathologists, many of whom regard all structures which are to them incomprehensible, as some type of degeneration product of the cell. Such a study, made with the best methods and the best technique that the zoological side can afford, should lead to an independent point of view and should give definite results which, together with those of the pathologist, the chemist, the physiologist and the surgeon, should give a clear conception if not a solution of the general problem of Carcinoma.

In the third place, to my mind the problem should be attacked from the physiological and chemical point of view, with especial reference to the possibility of specific activity of toxins of micro-organism origin.

In the fourth place, when the morphological side has yielded all its possibilities, the experimental side, strictly speaking, may well give some definite and conclusive results. Such experiments based upon the knowledge of the life-history of the possible organism would then produce results without loss of time, for by analogy with other

Protozoa we would know what phases of the life-history of the organism would give best results.

The first work that I wish to do in connection with the cancer problem is to make a thorough study of the morphology of the cell inclusions, using the most careful technical methods, and to compare these structures with the developmental phases of all kinds of Protozoa where such development is known. A great amount of literature has accumulated in regard to these cell inclusions, and many structures which have been described by various observers may well be taken as a basis for observations from the biological point of view, although such structures may have been variously interpreted as degeneration products, as secretions, or what not, by the various observers. Thus the work of Sawtschenko, based upon carefully prepared material and with accurate illustrations, and later the work of Borrel, based upon an equally efficient technique, have given a basis for my own observations on the carcinomatous cell inclusions. This morphological work is far from complete and is not yet in form for publication, but enough evidence has been independently acquired to justify the provisional assumption that these cell inclusions are neither secretions, as Greenough describes, nor degeneration products of the cell, as most pathologists very generally describe, nor are they modified centrosomes and spheres, as Borrel maintains, but phases of an organism belonging to the group Protozoa. This is based upon the discovery, not only of amœboid forms enclosed within the characteristic capsule which is typical of the so-called "Plimmer's bodies," but upon reproductive phases, upon nuclear changes and upon characteristic morphological protozoan structures. There is reason to believe that the capsule mentioned above is not a part of the organism but a more or less specific modification of the surrounding plasm through the action of a toxic substance created by the organism. Such a conclusion is strengthened, first, by the fact that when the inclusions are in the cytoplasm the capsules have the characteristic cytoplasmic staining reactions, while when these same structures are within the nucleus, where I have repeatedly found them, the capsules take the characteristic chromatin stains. Second,

by the fact that, with what may be interpreted as possible later stages of the organism, the capsule is much thicker than in the supposed younger phases, a fact which can be interpreted only as due to the continued activity of some formative cause.

While such structures justify the provisional assumption of a protozoan organism in cancerous tissue, they do not justify the contention that their presence is the cause of cancer, nor is there enough evidence as yet to indicate in what group of Protozoa the possible organism belongs. Feinberg, in a recent paper, lays himself open to criticism by his unproved assumption that these inclusions have a characteristic protozoan nucleus and he follows Korotneff, Behla and others in giving a new generic and a new specific name to the supposed organism, which, as *Histosporidium carcinomatosum,* he is unable to place in any known group of Protozoa. His principal argument—the structure of the nucleus—is weakened because of the complete oversight of the great numbers of Protozoa in which the nuclear structures do not agree with his " type." If this inclusion is an organism we may look not only for such " typical nuclei " but also for nuclear structures and nuclear processes like those of bacteria or certain of the lower Mastigophora, where a definite morphological nucleus is wanting and where structures are found which Hertwig has described under the name *Chromidien,* and which I have described as " distributed nuclei." It is certainly conceivable that, living as intra-cellular parasites, there is no need of a functional nucleus, except for reproduction, any more than a tapeworm has need of a digestive tract.

It might be of interest in the present place to point out one or two biological interpretations concerning the origin of tumorous growths in human tissues. It is quite difficult, indeed, to separate such interpretations from pathological conceptions, but in one or two cases at least the attempt has been made. Quite recently Boveri, studying the question of heredity on the cytological basis, was able to show that the chromosomes, which are definite chromatin structures of a certain size and always of the same number for the same species of animal or plant, have each a specific part to play in the organism.

Thus, in the egg cell of a sea-urchin, where the nucleus of the fertilized egg contains thirty-six chromosomes, if some of these chromosomes are removed, as Boveri was able to do by ingenious experiments, the result is a deformed embryo. Further, the deformity depends upon the nature of the chromosomes that are removed. Boveri concluded from these experiments that each chromosome of the egg defines a certain localized area or set of structures in the adult organism; and further, he maintained that should anything cause the displacement or removal of the chromosomes an abnormal development would result. Applying this result to the question of malignant tumors, Boveri assumed that the well-known atypical division figures of carcinomatous tissue give the chance for an irregular distribution of the chromosomes to the daughter cells; and, he argued, in this way the typical number and arrangement of the chromosomes are disturbed, with an abnormal growth as the result. Ingenious as this theory is, it nevertheless begs the question as to the origin of the tumor, for it leaves unexplained the cause of the irregular division figure and the continuation of such irregularity, which cannot be considered in any sense a normal process, and which therefore must be ascribed to something abnormal in the organization—possibly a toxin of organic origin, possibly an enzyme of other origin.

Quite a different hypothesis was offered last year by the writer and based upon experiments made on animals even more remote from the human organism than the sea-urchin. The experiments were undertaken with the purpose of ascertaining the length of time that a protozoan organism could live upon the same diet and without the intervention of the usual and normal sexual processes. A single individual of *Paramœcium caudatum* was isolated in a small chamber containing a limited supply of food medium, hay infusion. At the end of twenty-four hours the individual divided; that is, reproduced asexually, and two organisms were found the next day in the cell. Each was isolated as the first one was and treated in the same way, the result being four individuals at the end of forty-eight hours. These were again isolated and the process repeated day after day

and generation after generation for a period of twenty-three months, or until the race died out from what was unmistakably protoplasmic old age, in the 742d generation. Paramœcium had been studied in like manner previously by two different observers, each of whom found that the vitality of the organisms gave out at the end of the 150th to the 170th generation, when the entire race died. A similar experience threatened the cultures which I had undertaken, for at the end of such a cycle the individuals began to die at an alarming rate and showed unmistakable signs of physiological exhaustion. The survivors, however, were given a change of diet in the form of beef extract in place of hay infusion for one thing, while a simple salt (potassium phosphate) was also used. In both cases the result of the change was a renewal of physiological activity, or a rejuvenescence, and with the new potential of vitality thus obtained, a new cycle of 170 odd generations was started. The process had to be repeated at the expiration of this second cycle and a stimulus was again necessary to save the race. A third time the process was repeated, but the renewal of activity was not as satisfactory as the earlier experiences, and at the fourth period all efforts to rejuvenate were futile and the race died out from protoplasmic senility.

The point of this experiment in the present connection is that a stimulus of artificial nature gives a renewal of vitality to physiological processes which have become weakened through continued activity. An ordinary cycle of Paramœcium of 170 generations might be compared with a given tissue in the human organism, the difference being that the cell progeny from the primordial cell in Paramœcium remain separated, while in the tissue the progeny from the original cell remain connected and become differentiated. In the paper which was published last year the suggestion was made that such tissues run through their dividing activity at a certain period of life and become in respect to that function worn out. A stimulus of some nature may, like the change of diet in Paramœcium, or like the potassium phosphate, renew the vitality of some one or more of these worn-out cells and cause them to proliferate. Such proliferation at an unusual time and in the full-grown organism could give rise to but one result, namely, a pathological growth.

The point now arises as to the nature of the stimulus. A chemical substance, such as a toxin, might do it in the same way that potassium phosphate stimulates the worn out race of Paramœcieum, and the toxin might be produced by an included organism. That this toxin production is possible with protozoan parasites is demonstrated by the well-known case of Malaria, in which the pyrexial attacks are due to the liberation of substances produced by the malaria organisms.

It can do no harm certainly and it may lead to positive results to carry out a series of experiments upon the basis of the above hypothesis, and the morphological work will combine with the physiological and chemical to this end.

REPORT OF THE BIOLOGICAL CHEMICAL DEPARTMENT.

By G. H. A. Clowes, Ph. D.

The study of the cancer problem from a biological standpoint is one which must be approached from several different sides simultaneously in order to obtain a clear conception of its importance. Such work should be carefully elaborated and every detail confirmed by means of duplicate experiments before the results are published. A large amount of fruitless work has been carried out in the past, owing to the fact that individual investigators have frequently taken up a single phase of the subject, disregarding other possibilities than those which they themselves had in view, and have based their results upon single experiments which have subsequently proved to be incorrect. Bearing these facts in mind we laid down in a previous report a scheme of work to be followed out in this department so soon as it should be possible to carry on such work under favorable conditions. Since the establishment of our new Laboratory the work which had previously been confined to simple experiments, mostly with reference to various forms of parasites which were supposed to play a part in the causation of cancer, was extended to more elaborate experiments, many of them of a strictly chemical nature.

The subject was treated under three main heads: I. The study of Metabolism as it exists in patients suffering from cancer as compared with normal individuals and those suffering from other diseases. This portion of the subject involves study of the stomach contents, blood, urine, etc., and will be dealt with more fully at a later period. II. Experiments made with a view to obtaining evidence regarding the cause of cancer, and if a parasite should be that cause, of determining what is the nature of the parasite. Biological-chemical experiments of this nature are mostly micro-chemical and usually based upon theoretical considerations, and the evidence to be

obtained from them must be looked upon as more or less circumstantial. III. Attempts have been made to cure cases suffering from cancer by means of serum therapeutic treatment and the use of various chemical agencies, the probable value of which has been indicated by the experiments made under the head of Metabolism. Under this heading curative effects produced by the X-rays have been carefully studied with a view to discovering their mode of action.

The work included under the heading of I, "Metabolism," and III, "The Treatment of Cancer," is necessarily very complicated and slow in giving results. The frequent errors in diagnosis, even on the part of the most expert physicians, the death of patients and their removal from the hospitals, and the fact that our experiments are necessarily more or less confined to incurable cases, makes it necessary to be extremely conservative in any statements regarding results until those results have been established in a large number of similar cases, and until a sufficient length of time has been allowed to intervene in order to obtain definite data regarding the course of the disease.

Part I may be subdivided into:

a. Study of the secretions of the stomach in cancer as compared with the results found in other diseases and under normal conditions.

b. Examination of the blood of cancer patients with a view to discovering any abnormal constituents, either toxins or chemical products due to abnormal cellular metabolism; also a comparison of the relative proportion of certain constituents of the blood under normal and pathological conditions in which cancer and other related diseases are involved.

c. Study of urine and excreta, especially during the last stages of cancer comparing the proportions of the various normal and abnormal constituents at various periods of the disease with those found under normal conditions.

d. A chemical examination of various transudates and exudates found in patients suffering from cancer.

e. Chemical analyses of tumors themselves as compared with normal tissue, and an examination of such tumors from a toxicological standpoint.

f. A careful comparative study from a chemical standpoint of tumors supposed to be derived from the cells of other organs present in the body, with a view to proving whether these derived tumors possess the same properties and contain the same chemical bodies and enzymes as those cells from which they are derived.

A large amount of work has been carried out under each of these separate headings:

a. Study of from 30 to 40 stomach contents, 8 of which were diagnosed as cancer of the stomach. It has been established without any doubt that the hydrochloric acid secretion in the stomach is not in any sense proportional to the peptic activity; that hydrochloric acid is not necessarily absent in cancer of the stomach, and that the total absence of hydrochloric acid, accompanied by lactic acid, is not necessarily indicative of cancer. The writer has attempted in every case to fractionate the products of peptic digestion, and if possible to prove some relationship between the amount of so-called free and combined hydrochloric acid with one or more fractions of the digested proteids. In carrying out this work it has been observed that the methods ordinarily adopted in analyzing stomach contents are extremely faulty, certain constituents which are normally absent being included, while others which are normally present are incorrectly estimated and included in the wrong part of the analysis. It is not possible to go further into detail regarding this work at the present moment, but a paper fully covering the subject of the analysis of stomach contents, peptic activity and hydrochloric acid in the stomach secretions in cancer as compared with other diseases, and the bearing which these results have upon the whole problem of cancer metabolism will shortly be published in one of the medical chemical journals.

b. Exact analyses of the blood as a whole, of the serum and corpuscles, have been made in four cases of cancer; in each case the diagnosis had been confirmed either by an operation or autopsy. Also analyses of the blood of animals suffering from cancer have been made and these results have been compared with those obtained from a large number of normal individuals. In each case we

observed diminution in the alkalinity as compared with the normal. Chlorides and certain other constituents were undoubtedly high, while the fractionation of the nitrogenous compounds showed the presence of certain bodies which are probably not present normally, or at least in smaller proportions. Further enzymes, such as oxydases and toxins capable of affecting red blood corpuscles, were also considered, but so far, perhaps owing to the small amount of material at our disposal, it has not been possible to bring positive proof of any of these bodies being present in proportions deviating to any considerable extent from the normal. The difficulty of such an investigation either from a chemical or biological standpoint will be realized when it is remembered that the cachexia obtaining at the last stages of cancer is frequently complicated by secondary changes in the tumor itself, due to the destructive influence of bacteria, the excretory products of which seriously complicate the problem.

c. Urinalyses. Under this heading must be considered several long series of urinalyses carried out from day to day, frequently covering periods of three and four weeks, during which the greatest care has been taken to secure full twenty-four hour samples without any loss of material. In a few cases the influence of diet has been carefully considered, an exact record of the food consumed having been made, and on comparison of the analyses of the food and urine from day to day it has been possible to observe the progress of the patient. In dealing with this subject it has been our endeavor to arrive at exact results under three principal headings: 1. Variations of normal constituents of the urine in cancer. 2. The influence upon the katabolism of the organism produced by varying diet and the therapeutic treatment. 3. The presence of abnormal constituents, their proportions if considerable, and especially has it been our endeavor to discover some body or bodies characteristic of cancerous urine which might be made use of for the purpose of early diagnosis. Experiments have been frequently interrupted or have miscarried owing principally to the difficulty of controlling patients, but our results have on the whole been fairly constant, and it is to be hoped that in the course of the next few months we shall have accumulated enough material along these lines to justify publication. It has

already been found possible in certain cases to determine the location of the tumor from the nature and proportion of the bodies found in the urine. It must, however, be carefully borne in mind that many results of this sort are probably of a secondary nature, rather due to disturbance of normal cell metabolism than to the production of abnormal constituents by the cancer cells. The fact, for example, that cancerous urine is extremely toxic for animals has long been known, and repeating the experiments of previous investigators, we have been led to conclude that this action is due rather to the abnormal state of the patient, whose metabolism has been so interfered with that a large number of suboxidized bodies are excreted with the urine, which, if properly oxidized, would exert far less toxic action than to the influence of any specific toxin. We have also commenced series of experiments regarding the effect produced in the urine by the injection directly into the tumor mass itself of certain chemical substances.

d. Three peritoneal transudates have been examined chemically In one the exact secretion by this means of chlorides, of various nitrogenous constituents from day to day was accurately determined, and the figures obtained will be of value in the general study of metabolism which we propose to elaborate at a later date. Experiments made with this material on animals with a view to inducing immunity will be referred to later. It should be noted under this heading, as well as in the case of urine previously referred to, that a large number of investigators have described what they supposed to be unique chemical products characteristic of cancer which they had discovered and isolated. The repetition of their work by the writer has invariably led him to the conclusion that they had mistaken well-known normal products of metabolism for something of a more complicated nature.

e. The chemical analyses of ordinary tumors have not shown anything very remarkable or particularly worthy of interest, consequently very little time has been devoted to that branch of the subject. Also, on examination for toxins by disintegrating the tumor mass, filtering through a bougie under pressure, whereby bacteria, etc., are removed, it has not been found possible to produce any

marked toxic effects except in those cases in which a secondary decomposition of the tumor mass had taken place.

f. Investigation of chemical constituents of tumors derived from specific cells. Previous investigators have proven that tumors derived from the thyroid gland contain iodine and are capable of reacting in many respects as do the thyroids themselves. Bearing this in mind we examined a hypernephrom supposed to be derived from the adrenal, with a view to observing the nature of its chemical constituents and whether it contained a body capable of exerting the same effect upon the blood pressure as does the extract of normal adrenals. Unfortunately the only good specimen which has been put at our disposal had previously been placed in formaldehyde and subsequently in alcohol, so that the negative results which we obtained were only to be expected. The other cases which we examined proved on subsequent pathological diagnosis not to be hypernephromate. We are looking for fresh material in order to repeat our own experiments and also to confirm those recently published by Crofton. Making use of formaldehyde hardened material, we have been unable to obtain a differentiation of the tumor material from normal kidney and other tissues by means of his iodine reaction with the same facility that he claims for it.

II. Regarding the cause of cancer and the nature of the probable parasite. In studying biological problems involved in cancer from a chemical standpoint, with a view to establishing the exact nature of the disease, and if possible obtaining evidence regarding its cause, we have endeavored to free our mind entirely of the preconceived notions held by the majority of those who are working in this subject. The notions referred to are frequently based on observations made by means of the microscope on sections of tissue which, in the course of the hardening and staining processes to which they have been submitted, have undoubtedly undergone very considerable morphological and chemical changes so that no absolute significance should be attributed to them, whereas they are undoubtedly of very great value as a means of supporting evidence obtained in other ways. Strictly chemical work under this heading is almost entirely of a microscopical nature. An examination of yeasts and

protozoa of various types (Plasmodiophora Brassicæ) compared with fresh cancer material has been carried out, and most of the work under that head has been incorporated in previous reports made by Dr. Gaylord and will not therefore be considered at this stage. Certain cells normally found in cancer and known as mast cells have been investigated in hopes of determining their chemical nature and in that way obtaining some insight regarding their function in the tissue. The results of a series of such micro-chemical experiments, when completed, will be published in a microscopical journal and will, we hope, serve to bear out the statement previously made regarding the influence exerted by the chemical bodies to which the tissue is submitted during the hardening and staining processes.

III. As regards the cure and treatment of cancer, other than by means of the X-rays, a very little can be said at present. As stated above we have only been able to make use of inoperable cases, which, under normal circumstances, should be expected to succumb in the course of a few weeks or months as the case might be. We have tried the serum treatment, following the lines usually adopted in the treatment of other diseases in which the infective agent is known but without any marked result, which was to be expected when the probable nature of a cancer parasite is considered. In the paper preceding this, written by Dr. Gaylord, and dealing with the probable nature of a cancer parasite, it will be seen how completely such an organism deviates from bacteria and how impossible it is to draw any conclusions regarding its mode of development, so-called culture and mode of transmission, or regarding as a possible means of inducing an immunity, against it along the lines already developed in bacteriology. From various considerations it it is highly probable that any such organism has so much in common with the normal elements of the blood as to make an immunity established against it practically result in auto-intoxication. This is a subject, however, which is not sufficiently investigated at present and must be referred to a later period. The author has in the course of the last few months collected and abstracted all the literature bearing upon the subject of immunity in general, and especially all that which would have any possible bearing on the

cancer problem, and is firmly convinced that any attempt to treat that phase of the subject in the same way as previous problems in immunity have been handled will fail to yield results. Some entirely new conception of the whole problem must be evolved.

We have investigated the effect produced by normal sera and so-called immune sera. Also that of certain chemicals which we were led from our metabolism experiments to suppose would exert a specific effect upon the development of the tumor. These experiments have undoubtedly in a few cases retarded to a certain extent the development of the cancer and even produced a considerable diminution in size, and have also in certain cases alleviated the pain, but we are not very sanguine regarding such treatment and should not wish to suggest its general application at present. We shall, however, in the course of another year have ample opportunity to make some accurate observations under this head.

The treatment by means of X-rays is being fully dealt with by Dr. Park in another publication. In conjunction with that work we have made observations from time to time regarding the metabolism of individuals suffering from cancer who were undergoing the treatment. We are also at the present time carrying out a very elaborate series of experiments on normal and diseased animals with a view to arriving at a clear conception of the mode of action of the X-rays upon the tissue, the effects they produced in the blood and urine, etc., and from what we have so far obtained, it seems probable that we shall be able in the course of time to gain a clearer insight regarding the nature of the action produced by these physicial agencies in the living body.

To summarize the results obtained, it may be said that a large amount of work bearing on widely different phases of the subject is in the course of completion; only a few of the less important pieces of work have been entirely finished and much that has a very significant bearing upon the subject has barely been commenced. In the course of the last year, since our new laboratory was established, the greater part of the strictly chemical work, involving many hundreds of analyses, has been carried out. Such a work of necessity takes a considerable amount of time. It would

be useless to approach such a subject from any one point of view, as has been done by so many investigators previously without success. To cover the subject completely it was necessary to start the work upon a large scale, upon such a scale that it has been found impossible to arrive at any positive conclusions up to the present. This is partly owing to the difficulty of obtaining exactly that material which one most requires. In spite of the fact that we are situated in a so-called cancer district, the amount of material at our disposal is not so large as might be wished, and work on certain types of rare tumors must frequently be postponed for a year or more for want of material. Consequently it is our endeavor to carry on work continuously on that material which is most readily available, and in addition, when the opportunity offers to investigate those more unique cases which are hard to obtain. Owing to the fact that so many errors have been made in the past by the publication of results based on too small an amount of material we have resolutely adhered to our original intention of refusing to publish any results which have not received repeated confirmation. We have also made a point of confirming all data regarding normal conditions of metabolism where any question of deviation from the normal was involved, since the figures stated by pathologists are frequently extremely incorrect.

In conclusion it may be said that the work so far carried out in the Laboratory, together with the greater portion of the literature bearing directly or indirectly upon the subject, harmonizes with the views held by Dr. Gaylord regarding the probable parasite of cancer, as published in a previous portion of this report. The evidence which will be adduced in support of the theory from a biological-chemical standpoint, is of course indirect, but in such a case indirect evidence is of considerable value, and the fact that it is difficult to explain the proliferation of cancerous tissue from a physiological-chemical standpoint, without the intermediate action of some such organism foreign to the body itself (as has been attempted by some recent investigators) is in itself a support of the parasitic theory.

February 1, 1903.

TREATMENT OF CANCER.

By G. H. A. Clowes, Ph. D., and Herman G. Matzinger, M. D.

A series of cases suffering from cancer have been submitted to a chemical treatment based upon the results obtained in the chemical laboratory with reference to the metabolism of patients suffering from cancer. We should prefer not to make any definite statements on the subject at present, as sufficient time has not been permitted to intervene since the commencement of these experiments in order that proper observations should be made, but we have to record a considerable improvement in the condition of several patients, a disappearance of pain, and marked retardation in the development of the tumor mass, and in some cases a considerable diminution in its size.

Further details regarding this mode of treatment will, we hope, be elaborated in the course of the next year, when we shall be in a position to publish our experiments.

February 1, 1903.

A NOTE ON THE TOXIC AND VITAL THEORIES REGARDING THE CAUSATION OF CANCER AND THEIR BEARING UPON THE PARASITIC THEORY.

By G. H. A. Clowes, Ph. D.

The theory has recently been advanced in several prominent publications that the proliferation of the cells of malignant tumors may be attributed to the action either of toxins or of chemical bodies resulting from abnormal cell metabolism. This statement is usually made without further qualification, leaving the reader to form his own opinion regarding the exact nature of the reaction involved. It must, however, be borne in mind that a toxin or chemical body capable of producing the phenomena observed in cancer should scarcely be the product of the normal or abnormal metabolism of human cells, without the intervention of some external agency; and it is with the intention of showing that the phenomena in question may most readily be attributed to the intervention of some form of parasite that a few points worthy of interest will be briefly referred to at this stage.

If we are willing to assume (and it can scarcely be doubted in view of the existing evidence) that some toxic or chemical body plays an important role in causing the cells of malignant tumors to proliferate, the question may well be asked, From what source is this body derived and how does it exert its specific action on the cell? Three possible alternatives may be considered:

1. Some interference with its normal function gives rise to the production within the cell of a toxin or chemical body capable of exerting a specific action upon the cell and thereby stimulating it to abnormal development.

2. Some toxin, generated possibly at a considerable distance from the point at which the tumor commences but possessed of an affinity

for that particular type of cell, is absorbed by the latter and stimulates it to proliferate.

3. The parasite infecting the cell and itself proliferating and producing a toxin capable of exerting an irritating action on the host cell causes the latter to proliferate.

The first and second alternatives may readily be disposed of in view of the following facts:

A toxin can never (so far as we know) reproduce itself or aid in its own reproduction. It either produces no result, or it exerts a more or less pronounced action on the cell exposed to it; if that action is too great for the cell to overcome, the latter succumbs. If, on the contrary, the cell is capable of counteracting its toxic activity, an antitoxin will probably be produced. A similar line of reasoning applies to the action of a simple chemical body which is capable of exerting a poisonous action. It reacts with those groups in the cell protoplasm for which it possesses the maximum affinity, and if the quantity introduced is sufficient the cell is destroyed. If this is not the case, the chemical body in question, together with those portions of the protoplasm which have been disturbed by its action, are removed in the ordinary course of cell metabolism; and unless a fresh supply of the same body is introduced in continually increasing quantities the stimulation of the cell by this means ceases.

In view of these facts it is evident that even were it possible for a toxin or chemical body (produced under abnormal conditions within the cell itself) to stimulate the latter sufficiently to bring about proliferation (which is highly improbable) the body in question would rapidly become exhausted, or at least diluted to such an extent as to render further proliferation under its influence out of the question. As was stated above, such bodies are quite incapable of helping to reproduce themselves; the reverse would rather be expected. One is therefore in order to uphold the possibility of the first alternative (mentioned above) forced to the conclusion that the fresh cells derived from the original cell which first proliferated have inherited the power of reproducing within themselves that stimulating agent, toxic or otherwise, under whose influence they themselves will subsequently be forced to undergo further proliferation.

Such an assumption is quite unwarranted. No analogy for any such action exists in nature, and any such theory may be summarily dismissed in view of the fact that the principal difficulty which it presents (i. e., the source of supply of the ever increasing quantities of toxic material required to stimulate the increasing number of tumor cells) may so readily be explained by assuming the presence of a parasite, as will be shown later.

A second alternative, that the toxin in question is produced in an entirely different portion of the body from that in which the particular cells involved are located, may also be disposed of by means of similar arguments. It must be borne in mind that this toxin would have to exert a selective action; it would have to possess an affinity for one particular type of cells, but why then should it select any one particular cell, or, having selected that cell, why should it further show a preference for the derivatives of that particular cell after repeated proliferation has taken place? Further, the toxin in question would have to be supplied in ever increasing quantities from without the cell, for as stated in the argument brought against the possible production of a toxin or chemical body within the cell itself it is quite inconceivable that such a body introduced from without should lead to the continuous reproduction of itself within the cell in question and its derivatives. It is, on the contrary, highly probable that an antitoxin or antibody would be produced, or that the cells would become so accustomed to its action as to be less readily stimulated to proliferation than the surrounding cells of the same species. From these considerations it will be seen that when the cell undergoes subdivision in order to counteract the influence of any poisonous body to the action of which it may be exposed it is highly improbable that the derivatives of that cell would be endowed with the faculty of reproducing that particular type of poison, or that they would be more susceptible to its influence than are the surrounding cells of the same type. The opposite result might be expected in both cases.

The third and only explanation of proliferation of the cells of malignant tumors as being due to the action of some toxic body

which has any significance, or is in any way borne out by the facts with which we are acquainted, is that the cell in question has become infected with some type of parasite which itself proliferates and produces toxins which in their turn react upon the host cell, compelling it to undergo subdivision in self-defense. It must be borne in mind that the encounter taking place under such circumstances between the host cell and the parasite which has been introduced is one in which the excreta of the parasite play a very important part. It is by this means alone that the parasite is enabled to protect itself against the forces normally possessed by the cell whereby the latter is enabled to destroy and assimilate or eject any foreign body finding its way into its protoplasm. The parasite being once established naturally proliferates and its excreta and the toxins which it probably produces cause such inconvenience to the host cell that in order to diminish the number of parasites per cell and consequently the concentration of toxins the cell itself proliferates. It then becomes a question of the relative speed at which host cells and the parasites within them proliferate, and the relative toxicity of the excreta of the parasites as to whether the host cells by continual proliferation eventually succeed in entirely overcoming the parasites, or whether owing to a uniform and continuous subdivision both of host cells and parasites an exact condition of equilibrium is established; or whether as a third alternative the parasite succeeds in entirely exhausting the cell, in which case the parasite would in all probability form some type of permanent spore which would no longer produce toxins capable of affecting the surrounding tissue.

For such a mode of procedure we have a good analogy in the case of certain forms of paramœcia, which, on becoming infected by lower types of parasites, frequently proliferate and in that way are enabled to recover from the infection. (See Metchnikoff, *L'Immunité*, page 20.)

Another rather ingenious but extremely farfetched suggestion is that made by Foulerton, who attempts to account for the proliferation of epithelial cells by assuming that up to that point the cells in

question have been restrained in their natural tendency to develop by the action of some antibody induced by reactive materials which are continually passing into the system from organs undergoing degeneration. This line of argument is so involved and introduces so many assumptions for which we have no analogy that it is hardly necessary to consider it in comparison with the much simpler explanation of toxic activity previously referred to in connection with the parasitic theory. It is, however, our intention to treat this subject more fully at a later period.

It must be borne in mind in dealing with this phase of the subject, just as it has been shown in Dr. Gaylord's contribution to this report, that the question regarding the existence or non-existence of a parasite in cancer cannot be decided by making use of generally accepted bacteriological principles, so it will probably be found necessary to treat the questions involved in toxic and chemical activity in a manner entirely different to that employed so successfully at the present moment in dealing with those problems in which bacteria and their products are concerned.

February 1, 1903.

A STATISTICAL STUDY OF A RURAL CANCER DISTRICT IN THE STATE OF NEW YORK.

By Irving Phillips Lyon, M. D.

BROOKFIELD, MADISON COUNTY, NEW YORK.

I selected this place for investigation as the result of a detailed compilation and analysis of the mortality statistics published in the Monthly Bulletin of the New York State Board of Health for a period of years, the substance of which analysis showed that, of the various sanitary districts into which the State is divided, the East Central District* presented the highest death-rate from cancer, and of the many specified localities in this district, for which separate figures were given, the township of Brookfield, in Madison county, showed the highest cancer mortality rate. In fact, Brookfield** was distinguished from all the other specified localities of the district by a death-rate from cancer which was not even approximated by any other place, and this rate was determined on the basis of the entire period, 1887-1900.

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*For the year 1900 the cancer mortality per 100,000 of population in the different sanitary districts ranged from a minimum of 59.2 to a maximum of 82, as follows:

1. Adirondack and Northern District, 59.2 per 100,000 population.
2. Maritime District, 63.5 per 100,000 population.
3. Lake Ontario and Western District, 64.9 per 100,000 population.
4. Southern Tier District, 66.8 per 100,000 population.
5. Hudson Valley District, 69.1 per 100,000 population.
6. Mohawk Valley District, 71.9 per 100,000 population.
7. West Central District, 73.4 per 100,000 population.
8. East Central District, 82 per 100,000 population.

Whole State, mean, 67 per 100,000 population.

**The Brookfield death-rate from cancer per 100,000 population for the period 1887-1900 was 149, based upon the returns published in the Monthly Bulletin of the New York State Board of Health. The highest rate for any other specified locality in the East Central District was approximately 102 (Delhi).

Having thus determined a locality of remarkable cancer mortality, I went to Brookfield in December, 1901, and again in May, 1902, and made a careful personal study of the local cancer incidence and of the various special conditions and factors that might be related to it.

Description of Brookfield.—The township of Brookfield lies close to the center of the State of New York, in Madison county. Its extent is roughly ten by eight miles, embracing approximately seventy-five square miles of territory. The country is very rough and hilly, partly wooded, and generally covered with poor farm lands and grazing hillsides. It is well drained from its hillsides into occasional brooks and small streams. Agriculture* and dairy farming are the only occupations of the people. There are no factories in the township. The population of the entire township in 1900 was only 2,726, of which number 485 lived in the village of Brookfield. Besides this principal village, the township includes the village of Leonardsville, somewhat smaller in population than Brookfield village; North Brookfield village with about 200 inhabitants, and the hamlet of South Brookfield, with a few houses clustered at crossroads. The township of Brookfield is therefore strictly rural.

Collection and classification of statistics.—I began my study by an investigation of the official register of births and deaths in the town clerk's office. I made a transcript therefrom of every death certificate in which the immediate or the accessory cause of death was assigned as cancer or malignant tumor of any variety. I did the same for all cases in which the assigned causes of death, where inexactly stated, suggested cancer as the real cause. With these transcripts in hand I visited the physicians who had signed the original death certificates and made a thorough canvass of the

*There has been claimed to exist, by certain writers, a possible etiological relation to cancer of a disease in cabbages, turnips, beets, etc., known as "clubfoot disease," "root disease," etc., this plant disease being caused by a microorganism called *Plasmodiophora Brassicæ*. It is not inappropriate, therefore, to mention here that "clubfoot disease" has extensively prevailed in Brookfield and the surrounding country and has been known, in some instances, to destroy a large part of a farmer's cabbage crop.

medical history, symptoms, signs and facts relating to each case. In a small minority of cases in which the original medical attendants were dead or inaccessible I either accepted the records at their face value or, where possible, obtained confirmatory or negatory evidence from the other living practitioners, who as consultants had had personal knowledge of the cases in question. As the result of this cross-examination of the various physicians I determined the actual number of deaths in which they affirmed and insisted upon cancer (including all forms of malignant tumor) as the cause of death either immediate or accessory, and I completed my records on this basis. I included in this enumeration all cases in which a malignant growth existed in the patient at the time of death, whether the physician regarded such malignant growth as the primary and immediate cause of death or as secondary and accessory to some other complications or terminal infection. For it seemed to me immaterial whether, with a general incurable and fatal malignant growth, the patient actually died from the immediate effects of this disease or in addition had and succumbed to nephritis, cerebral hæmorrhage, pneumonia, influenza or other terminal complication.

Accepting then all cases of death in which cancer was diagnosed and affirmed by the physicians, I obtained records of 84 such cases dying in Brookfield during the fifteen-year period, 1886-1900.* The number of deaths assigned to cancer as the cause by the monthly Bulletin of the New York State Board of Health for the same period was 70, 14 less than the number that I found was properly so assignable. This difference is due chiefly to the method employed in the office of the State Board of Health of assigning cases to that cause which is given in the death certificate as the "immediate" cause of death, whether the immediate cause be given as "grippe" and the accessory cause as "cancer" or vice versa. My figures are therefore higher than the State statistics by 20 per cent.

Sex and anatomical distribution.—By sex the 84 cases of cancer were divided into 35 males and 49 females, a usual ratio of the two sexes. The involvement of organs by sex is shown in Table I. Nothing unusual is noted in this distribution.

*The official records were incomplete prior to 1886.

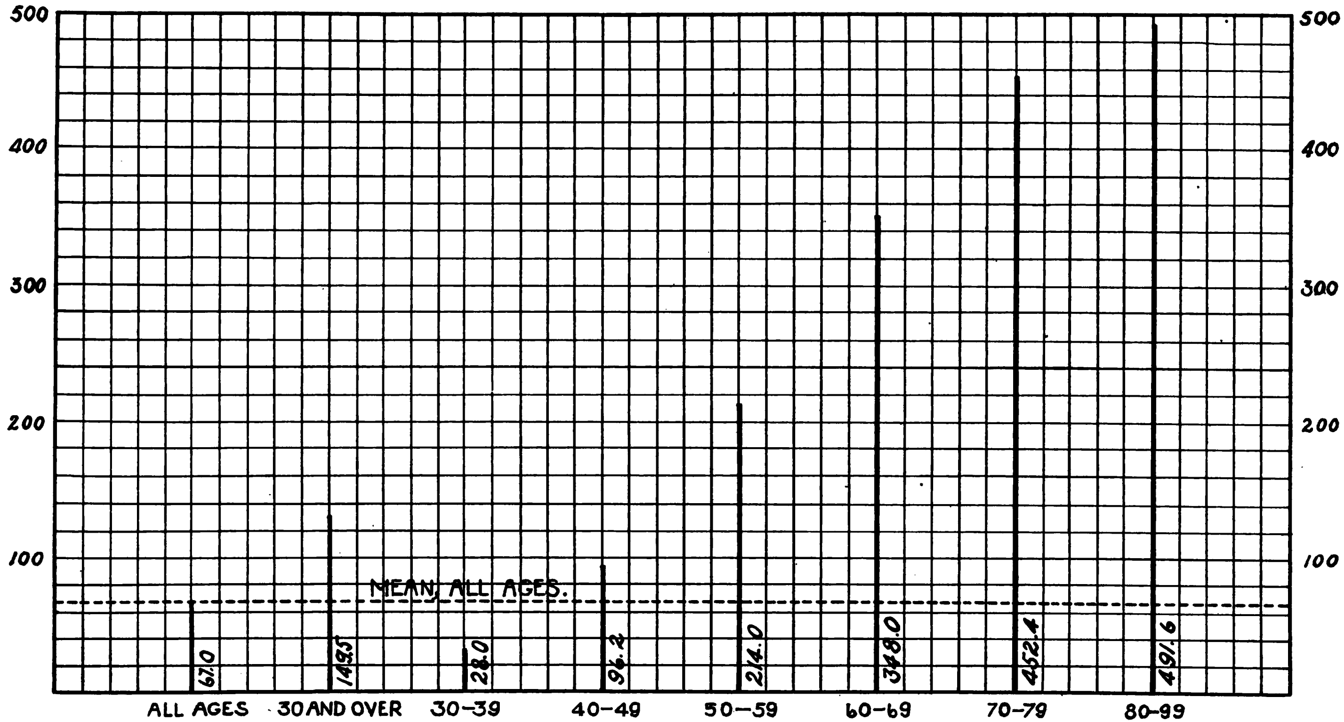
Comparison of cancer death-rates in Brookfield, State of New York, and registration area of United States.—We have then 84 cases dying from cancer in Brookfield during the fifteen-year period, 1886–1900. The number of deaths from all causes in the same period, determined from the town-clerk's official register, was 719. The mean annual population of Brookfield for this period, determined from the United States census, was 3,076. A comparison of these figures shows a most striking and remarkable cancer mortality rate. Thus a mean annual population of 3,076 showed a mean annual mortality of 47.93 from all causes and of 5.60 from cancer, or an annual death-rate from cancer of 1.82 per 1,000 of population. The cancer mortality compared with the general mortality showed one death from cancer in every 8.559 deaths from all causes—11.68 per cent.

How remarkably high this cancer rate is may better be appreciated by comparing it with the corresponding rates for the State of New York, as a whole, and for the census registration area of the United States, the figures for the latter two areas being for the census year 1900 and both being computed from the United States census. Thus compared the annual cancer death-rates per 1,000 of population were for Brookfield, 1.82; for the State of New York, 0.61, and for the United States (census registration area) 0.60, the Brookfield rate being therefore about three times the rate for either of these larger areas. If we take the Brookfield rate obtained from the cancer deaths of Brookfield as given in the Monthly Bulletin of the State Board of Health (1.51 per 1,000 of population) the Brookfield rate is found to be about two and one-half times the rates of the larger areas, or, exactly stated, the ratio of the Brookfield rate to that of the whole State of New York is 2.47 : 1.00.

Are there any general factors that may, in part, account for the high cancer death-rate in Brookfield?—How can this remarkable cancer death-rate, two and one-half times the normal, be accounted for? Are there any well-known factors, recognized by vital statisticians, that may be supposed to have influenced it, or must we seek its explanation entirely outside of such general factors in special and at present unknown or conjectural factors of etiology? Among such

CHART I. *Geographical Representation of the Influence of Age on Cancer Mortality.*

Deaths from Cancer in Each Age Group, per 100,000 Population of Corresponding Age Group, for Massachusetts, in 1895.*



* Based on "Statistics of Cancer in Massachusetts" by W. F. Whitney, M.D., published in the Thirty-Second Annual Report of the State Board of Health of Massachusetts.

recognized general factors, *longevity* and *error in diagnosis* must be considered in relation to the cancer death-rate, and I shall attempt to demonstrate that each has been operative in determining a part of the cancer mortality in Brookfield.

Influence of longevity on cancer mortality in general.—The relation of age to cancer mortality is too well known to require more than brief mention. A glance at Chart I will show graphically how rapidly cancer death-rates increase for each added decade of life. Thus, for Massachusetts, in 1895 the cancer death-rates per 100,000 of population of corresponding ages increased from 28 for the fourth decade of life to 96 (3.4 times) for the fifth decade; to 214 (7.6 times) for the sixth decade; to 348 (12.4 times) for the seventh decade, and to 452 (16.1 times) for the eighth decade. The increase is sustained through each succeeding decade of life.

Longevity in Brookfield.—Brookfield is a poor rural community, in which a livelihood is with difficulty obtained. As a result there is no increase of the population by immigration, but a continued loss by the emigration of the youth. The birth-rate is low. For the fifteen years 1886-1900 the births exceeded the deaths by only 38. The population has thus decreased, as shown by the United States census, viz., 1880, population, 3,685; 1890, population, 3,260; 1900, population, 2,726. Those who are left to care for the farms and the homes are the *adults, who,* living a simple life in a salubrious climate, *live to advanced age and die old.* The truth of this assertion if fully confirmed by the figures for Brookfield given in Tables II and III, and is made the more striking by comparison with the corresponding figures for the United States registration area. The average age at death from all causes for Brookfield in the period 1886-1900 was 54.4 years,* contrasted with 35.2 years for the registration area of the United States for the census year 1900. Sixty-one per cent of all deaths from all causes in Brookfield occurred in persons over the age of 55 years contrasted with 31 per cent (about one-half) for the United States registration area. For the age of 65 years and over, the corresponding figures for Brookfield and for the United States were, respectively, 49 per cent and 21 per cent. Exactly the reverse

*Determined from the death-records of the town clerk's official register.

is shown for the infant and child mortality of Brookfield compared with the United States. In Brookfield only 17 per cent of deaths occurred under the age of 20 years; in the registration area of the United States, 37 per cent, more than double the rate in Brookfield. Under the age of 35 years (the period of life of relative cancer immunity) only 25 per cent of deaths from all causes in Brookfield occurred, whereas for the United States registration area 50 per cent occurred in this period of life.

Influence of longevity on the cancer mortality of Brookfield.—With the proof then that longevity must have been an important factor in determining the high cancer mortality of Brookfield, what part of this cancer mortality can be accounted for solely by the longevity of the population? This question cannot be answered at once in terms of cancer death-rates per 1,000 of population, by age periods and by sex, for the data for such calculations are not obtainable. We can, however, obtain an answer to this question by indirect means and with a fair degree of accuracy.

If we assume that the cancer period of life is from 30 years of age upward—and this assumption* is approximately correct—it is possible to ascertain for various large bodies of population what percentage of all deaths over 30 years of age is represented by deaths from cancer in the same age period, and thus to establish a certain standard of cancer mortality which we may regard as normal. With such a standard of normal we may compare the corresponding percentage of cancer deaths to total deaths over 30 years of age for Brookfield and thereby obtain the excess above normal in Brookfield.

Tables IV and V contain the figures of this calculation. There is shown a remarkable agreement of the figures for the State of New York, the census registration area of the United States and the New England States. Thus the percentages of cancer deaths to all deaths over 30 years of age for these three areas are, respectively, 6.04, 6.17 and 6.25. So nearly identical are these percentages that one must be impressed, I think, with the view that no element of

*So far as Brookfield is concerned, this assumption holds absolutely true, as no deaths from cancer under 30 years of age were recorded.

chance, but rather a general law of proportion, determines them; i. e., determines a standard of normal.

The marked variation of the figures for Brookfield* from this standard of normal is striking and at once determines the excess over normal of the Brookfield cancer mortality. Thus, as shown in Table V, the ratios of the Brookfield figures to the figures for New York, the United States and the New England States, for all ages over 30 years, are, respectively, 2.08 : 1, 2.04 : 1, and 2.01 : 1; i. e., almost exactly double. And in estimating these ratios I have not used my own determination of the number of deaths from cancer in Brookfield (84 cases) but rather the figures (70 cases) in the official records of the State Board of Health, for manifestly in comparing rates such rates must have been based on a tolerably uniform system of collection and classification in order to be properly compared. And that there may be no misunderstanding of what follows hereafter in this paper I shall say here, once for all, that in comparing the Brookfield cancer death-rate with the corresponding cancer death-rates of other places I have made all estimates of the Brookfield rate on the basis of the 70 deaths from cancer, as given in the official records of the State Board of Health, and not on the 84 cases as determined by my special investigation.

We find, therefore, that the gross cancer mortality of Brookfield, for all ages, is materially reduced by making due allowance for longevity, and that, after making this allowance, the Brookfield cancer rate is still 2.08 times the corresponding rate for the entire State of New York, which (latter) may be taken as the standard of normal. Therefore, of the 70 deaths from cancer in Brookfield, only

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*The law of proportion, determining the standard of normal of cancer deaths to total deaths over the age of 30 years, is strictly applicable only to *similar large bodies of population whose mortality statistics are classified on a common basis.* For with a small population variations from year to year, due to exceptional local conditions, might introduce an appreciable error, which would not be the case with large aggregates of population in which the variations of the component parts are leveled in the average for the whole. In the case of Brookfield, however, the mortality statistics were classified by the State Department of Health on the same basis used for the entire State of New York, and any exceptional variation for a single year has been avoided by taking the mean for a period of 15 years.

33.5 (12.61 : 6.04 : : 70 : x = 33.52) can be accounted for by longevity, and 36.5 remain to be explained by factors other than longevity.

Other factors than longevity influencing cancer mortality in Brookfield.—To account for this excess of 108 per cent, or 36.5 cases above the normal, after making allowance for longevity, we must seek other factors. Evidently among such other factors *error in diagnosis* must be carefully considered.

Error in diagnosis as a factor in the cancer mortality of Brookfield.—Among the active practitioners of medicine in Brookfield I found several conscientious and intelligent physicians, men above the professional ability usual in such a place. Of some others, however, this may not be said. There were physicians who had signed death certificates whose knowledge of medicine was less than meager and whose ideas of diagnosis would have little value.* Moreover, there were certain " cancer specialists " who professed to cure cancer, without the use of the knife, by means of secret preparations applied locally and administered by mouth as " blood cures." The diagnosis of cancer was confirmed in one case by microscopic examination, and in 11 cases by post-mortem section, making only 14 per cent of the diagnosis of cancer determined by means that would be regarded as satisfactory. My confidence in the approximate accuracy of the diagnosis in a part of the cases diagnosed as cancer was therefore shaken, and I determined to ascertain if possible what part of the entire 70 cases could be accounted for by excessive error in diagnosis.

It might seem, on first thought, that such a determination with any degree of accuracy could not be made. However, I found a means to this end that I believe will be accepted as reasonably satisfactory. It depends on the principle of comparing the Brookfield cancer mortality with that of an adjoining similar town, *in both of which places the factors of longevity and error in diagnosis were relatively equal and, therefore, negligible,* as a result of which com-

*As an example of diagnosis, note the following verbatim extract from one of the death certificates, signed by two physicians: *Immediate cause of death:*—" Rupture of a hydatid into stomach which drowned her by strangulation (5 minutes)."

parison the excess of cancer mortality in Brookfield over that in the adjoining town would represent the part of the Brookfield cancer mortality that was due to factors other than longevity and excessive error in diagnosis. As the part attributable to longevity alone has already been determined, the part due to excessive error in the diagnosis (above the average amount of error in the whole State) can be found by subtraction. The principle of this method cannot be criticised, provided the condition of similarity of the two towns in the respects noted to be a fact. It remains for me, therefore to prove the similarity in the points named of Brookfield and the adjoining town selected for the purpose of the comparison.

The town selected for comparison is Plainfield,* immediately adjoining Brookfield on the east. All that I have said about Brookfield, as to its general character, topography, cultivation, occupation of its people, low birth-rate, emigration of its youth, declining population, longevity of the people and qualifications of the physicians, applies with equal force to Plainfield. The two towns are identical in all these respects. As to longevity and qualifications of the physicians, I must be more specific in order to fortify the general assertion just made. The population of Plainfield was in 1890, 1,025; in 1900, 897—a loss of 12 per cent. Brookfield lost in the same period 16 per cent. The annual death-rate per 1,000 of population during the period 1886-1900 was in Plainfield, 15.4; in Brookfield, 15.5. The average age of death from all causes of death during this period was in Plainfield, 55.1 years; in Brookfield, 54.4 years—almost identical. It is apparent, therefore, that so far as longevity is concerned in the influencing the cancer mortality there is no essential difference between the two towns. As to the qualifications of the physicians as bearing on the amount of error in diagnosis in each place, *the physicians of the two towns are the same.* The two

*Plainfield is not one of the specified localities for which separate mortality statistics are given in the Monthly Bulletin of the New York State Board of Health. I therefore was compelled, in order to obtain the required date, to go through the official register of deaths in the town clerk's office and extract therefrom the facts that I needed. In the deaths from cancer accepted by me I included only such as would have been assigned to cancer as the cause by the State Board of Health. The cancer mortality of Plainfield thus determined may therefore properly be compared with that of Brookfield.

towns together constitute a single unit of territory in the practice of the physicians. One death certificate only out of 16 in Plainfield, in which cancer was assigned as the cause of death, was signed by a physician whose name did not also appear on death certificates of cancer cases in Brookfield. It is therefore plain that whatever degree of error in diagnosis entered as a factor into the cancer mortality of Plainfield must have effected equally the cancer mortality of Brookfield.

Having thus demonstrated the proposition that the towns of Brookfield and Plainfield are exactly similar in respect to the influence of both longevity and error of diagnosis on the assigned cancer mortality of each place, I shall now proceed to compare their respective cancer mortalities in order to determine the excess of the Brookfield cancer mortality over and above that of Plainfield, and thus the exact portion of the Brookfield cancer mortality that must be assigned to causes other than longevity and excessive error in diagnosis combined.

The per cent of cancer deaths to total deaths over the age of 30 years in Brookfield was found to be 12.61 (70 in 555); the corresponding per cent for Plainfield I found to be 8.64 (16 in 185). If two of the 16 deaths from cancer in Plainfield be excluded from consideration for the purpose of this calculation because these two cases only among the 16 had a history of cancer in other members of their respective families, the per cent of cancer deaths to total deaths over 30 years of age in Plainfield is reduced from 8.64 to 7.56. I have excluded these two cases from present consideration in order to exclude from the Plainfield figures any influence of heredity, for reasons that will be appreciated when we come to the question of heredity as a factor determining the development of cancer in families with a cancer history. Comparing then these percentages for Brookfield and Plainfield, we have the ratio: 7.56 : 12.61 : : 1.00 : x (= 1.667).* The Brookfield cancer mortality

*This ratio and the deductions therefrom depend on the assumption that the entire Plainfield cancer mortality, except the two cases with a family history of cancer, is explained by the two factors, longevity and excessive error in diagnosis. Heredity, as an influence, has been excluded, so far as possible, for I made exhaustive inquiry into the family histories of all the cases and obtained a positive history of cancer in only two of the

is thus found to be 1.667 times that of Plainfield, after allowing in each for the combined influence of both longevity and excessive error in diagnosis; i. e., the Brookfield cancer mortality (70 cases) is 1.667 times the cancer mortality assignable to the combined influence of longevity and excessive error in diagnosis. Hence the following equations:

$$1.667 : 1.000 :: 70 : x \ (= 41.9 \text{ cases})$$
$$1.667 : 0.667 :: 70 : x \ (= 28.0 \text{ cases})$$

Therefore, 41.9 out of the entire 70 cases of cancer in Brookfield can be accounted for by longevity and excessive error in diagnosis. As 33.5 cases were determined as the number due to the influence of longevity alone, therefore 8.4 cases may be assigned to excessive error in diagnosis over and above the average error in the State of New York as a whole. There remain at least 28 cases not due to these factors and therefore to be accounted for by other influences.

What factors, other than longevity and error in diagnosis, have operated to produce the excess of cancer mortality in Brookfield?—Heredity and consanguinity.—In answering this question I realize that I have the most difficult part of my task to perform, in which I may not expect that my own conclusions will meet with the approval and acceptance of all. I must therefore ask the indulgence of those who disagree with me when I assert my own belief that heredity and consanguinity are the special factors that have operated with peculiar force in Brookfield to produce the excess of cancer mortality over that attributable to the factors already considered.

The truth of the assumption of a direct influence of heredity in determining the development of cancer in families can be neither absolutely proved nor disproved in the present state of our knowledge. It is conceivable that multiple cases of cancer in a family may be the result of (1) hereditary predisposition, (2) longevity, by which the various members of a family live to the cancer period of

16 cases, and these two cases I rejected in making the calculations. I believe, therefore, that the assumption made is close to the truth. However this may be, we have at any rate given to excessive error in diagnosis the maximal credit possibly due to it as a factor. Therefore, the 28 Brookfield cases is the minimum attributable to factors other than longevity and excessive error in diagnosis.

life, (3) mere chance* (4) infection with a hypothetical parasite, (5) other unknown etiological factors, or (6) any combination of two or more of these several elements. I shall not in this place engage in the controversy that is now waging over the etiology of cancer. The opinion held by each on the chief question involved in this controversy will naturally influence his answer to the question whether any part of the Brookfield cancer mortality may have depended on the influence of heredity. I would have no bone of contention to pick with anyone were he to attribute to this factor no part whatever of the excess of cancer mortality in Brookfield. For my own part I have no hesitation in asserting my belief in the reality of a heredity influence in determining the development of cancer in certain families. Holding this view, then, I should attribute to the influence of hereditary predisposition to cancer the excess of cancer in Brookfield that is not otherwise explained, because, as will be seen directly, a family history of cancer was a most prominent and noteworthy feature in a large part of the Brookfield cancer cases, and because no other special cause could be found to explain the local excess of cancer in Brookfield.

In order that full justice be done to the divergent views of etiology, I may add that the acceptance of heredity as a factor in cancer mortality does not necessarily commit one against the parasitic theory, for it is conceivable that hereditary predisposition to cancer may be simply hereditary susceptibility to infection with a hypothetical cancer parasite according to the analogy of certain other diseases. On the other hand, heredity may represent a congenitally transmitted tendency to a special cell proliferation—i. e., cancer—independent of any special infection. The ultimate explanation of heredity in cancer production may therefore be considered an open question.

The relation of family history of cancer to certain of the Brookfield cases of cancer is shown in Table VI. This table includes only such of the Brookfield cases in which it was practicable in the short

*For an able discussion of the possible bearing of chance on the occurrence of several cases of cancer in one family, see King, quoted in Newsholme's *Vital Statistics*, 3d edition, pp. 248-249.

time at my disposal to work out family histories and genealogies to a certain extent in the first and sometimes the second and third generations. I do not assume to exclude in many of the cases not mentioned in this table similar relations, for I was limited in time and opportunity to about two weeks' study, and in this time I had much more than such relations to investigate. Twenty-seven of the 70 Brookfield cases of cancer are included in this table. Of the remaining 43 cases not included, in many no special inquiry was made; in others the information obtained as to family history of cancer, multiple cases in one house, etc., was either indifferent or negative (denying such relations). It is apparent, therefore, that the relations shown for the cases mentioned in the table may not logically be assumed to hold for the larger number of cases not thus mentioned. Nor would I give the impression that the facts noted in Table VI in regard to the Brookfield cancer cases therein mentioned are in any sense complete or exhaustive of the subject. They represent simply the facts that I succeeded in obtaining in a somewhat cursory and hurried investigation. For much of this information I am indebted to Dr. H. Clift Brown of Brookfield, whose courteous and generous assistance I take pleasure in acknowledging. I am also indebted for material assistance to Dr. O. L. Southworth of Plainfield, Dr. O. W. Burhyte of Brookfield, and Dr. C. H. Chesebro of Unadilla Forks.

Twenty-seven of the entire 70 Brookfield cancer cases (38.5 per cent.) are included in Table V. *Of these 27 cases, 23 show a history of cancer in other closely related members of their families, and only four fail to show other family cases.* In one family, for a marked example, no fewer than seven cases of cancer occurred in three generations, four of them being in a single generation, and all the seven victims, except two, living and dying in different towns. One can hardly fail to be impressed by the figures cited and even more by a perusal of the table of facts from which these figures are summarized. To some it may seem no mere coincidence that 23 cases are cited in which a family history of cancer was demonstrated, and that only 28 of the Brookfield cancer cases were left to be accounted for by factors other than longevity and error in diagnosis.

These numbers are very nearly equal, and the equality might be even more exact were the family histories of the other Brookfield cancer cases known. I therefore submit to the judgment of those interested the decision of the question whether heredity really is the factor that determined the excess of 28 cases in the cancer mortality of Brookfield over and above the possibility of explaining by reference to longevity and error in diagnosis.

Consanguinity, with reference to heredity, must be taken into account in Brookfield. For not only has there been no infusion of new blood in the people of this small country town, but a considerable portion of the population has for generations belonged to a strict religious sect known as *Seventh Day Adventists,* among whom there has undoubtedly occurred much inbreeding as evidenced by the names of parents in the death certificates and by information gleaned by conversation with the people.

Before dismissing the subject of heredity and consanguinity, I wish to state a few further facts in support of the view that these factors are the real cause of the excess of cancer mortality in Brookfield. Compared with the neighboring country towns, which resemble Brookfield in their general characteristics,* Brookfield stands preeminent in its cancer mortality, though all of these towns show an increased cancer mortality compared with the entire State of New York as a standard. The per cent of cancer deaths to all deaths for all ages was in the State of New York, 3.42 (1900); in Brookfield, 9.73 (1886-1900); in Plainfield,* east of Brookfield, 6.0 (1886-1900); in Bridgwater,* northeast of Brookfield, 5.1 (1888-1901); in Edmeston,* southeast of Brookfield, 5.1 (1887-1901); and in Hamilton,† west of Brookfield, 5.1 (1887-1900). The towns surrounding Brookfield are therefore fairly uniform in their cancer rate as opposed to Brookfield. In none of these towns was I able by personal investigation to find any pronounced predominance of a family

*"Clubfoot disease" in plants prevailed equally in Brookfield and the surrounding towns.

†In Plainfield, Edmeston and Bridgewater, towns not specified in the Monthly Bulletin of the State Board of Health, I obtained the rates by a personal investigation of the registers of death. The rate for Hamilton is calculated from the statistics of the Monthly Bulletin.

history of cancer *within recent years.* I make this last qualification because in the adjoining towns of Plainfield and Edmeston I did obtain a pronounced family history of cancer in certain families living in a limited area of the town for many years ago; but such family cases had not occurred to any marked extent within the period of my investigation, 1886-1900. The sect of the Seventh Day Adventists was practically confined to Brookfield.

"*Cancer houses.*"—I was able to obtain a history of two or more cases of cancer occurring in each of nine houses in Brookfield. Such houses have been called by writers "cancer houses," and have been cited in corroboration of the theory of a parasitic origin or etiology of cancer, on the ground that they represented instances of local infection. An analysis of the facts presented in Table VI shows that, of the nine "cancer houses," in only four were the multiple cases occurring therein non-related by blood, and of these four in only one instance was there an absence of a family history of cancer in the immediate family for at least one member of the group in the same house. These facts are better shown by Table VII, adapted from Table VI, and support still further a belief in the influence of heredity.

"*Cancer foci.*"—I was able to discover no special locations or spots of concentration of cancer in Brookfield, unless the houses with multiple cases be so regarded.

Husband and wife cases.—With reference to this interesting relation of cancer, four instances were noted. In two the husband and wife lived together and died in the same house; in two they lived together during married life and died in different houses. In the former two instances the intervals separating the deaths of husband and wife were two and five years; in the latter two instances, three and eight years respectively. Of these four couples a family history of cancer in the immediate family for at least one member of the couple was absent in only one case; in one instance there was a family history of cancer for each member of the couple, and in two instances for one member only. There were no instances of cancer of the genitals among these cases.

Conclusions.—From the foregoing considerations I have reached the following conclusions: Brookfield is credited with a remarkably

high cancer mortality in the official statistics of the New York State Board of Health. An analysis of the cases shows that a considerable portion of the excess is explained by the two factors, longevity and error in diagnosis, and the remainder is probably due to the marked influence of heredity and consanguinity.

TABLE I.—*Anatomical Location of Cancer, by Sex, in Brookfield Cases for Period, 1886-1900.*

			Males.	Females.	Persons.
External	Face		2	....	2
	Nose		1	....	1
	Hand		1	....	1
	Axilla		......	1	1
	"Skin"		......	1	1
Sex organs and breast	Male	Penis	1	....	1
		Prostate	2	....	2
	Female	Uterus	......	10	10
		Ovary	......	1	1
		Breast	......	8	8
Alimentary canal and accessory organs	Upper	Mouth	......	1	1
		Jaw	2	....	2
		Larynx	......	2	2
	Abdomen	Stomach	16	17	33
		Liver	5	3	8
		Intestine	4	3	7
		Abdomen	1	2	3
Total			35	49	84

TABLE II.—*Age Distribution of Deaths from All Causes and of Deaths from Cancer in Brookfield, Period, 1886-1900.*

	All ages.	4-	5-9.	10-14.	15-19.	20-24.	25-29.	30-34.	35-39.	40-44.
Total deaths	719	80	10	13	22	13	24	21	24	20
Cancer deaths	84	0	0	0	0	0	0	3	5	6

	45-49.	50-54.	55-59.	60-64.	65-69.	70-74.	75-79.	80-84.	85-89.	90-94.	95-99.	Unknown.
Total deaths	24	28	22	63	64	79	72	80	41	14	3	2
Cancer deaths	5	4	9	8	17	10	7	6	3	1	0	0

TABLE III.—*Per Cent* of Deaths from All Causes and of Deaths from Cancer in Different Age Periods for Brookfield for Period, 1886-1900, and for the United States Census Registration Area, for 1900.*

	Age Period.						
	1-19.	20-24.	25-34.	35-44.	45-54.	55-64.	65 and over.
Total deaths:							
Brookfield	17	1	6	6	7	11	49
United States census registration area	37	4	9	9	8	9	21
Cancer deaths:							
Brookfield	0	0	3	14	10	20	52
United States census registration area	0	0	3	12	22	26	33

* Percentages expressed in whole numbers, fractions omitted.

TABLE IV.—*Per Cent of Cancer Deaths to Total Deaths at Different Age Periods.*

PLACE.	Time.	All ages.	All ages over 30.	30-39.	40-49.	50-59.	60-69.	70-79.	80 and over.
New York State *a*	1900.	3.42	6.04	2.7	6.8	8.8	8.3	5.4	2.6
United States census registration area. *a*	1900.	3.45	6.17	2.8	7.1	9.3	8.1	5.4	2.8
New England States *b*	1895.	3.53	6.25	3.09	6.14	9.77	8.36	5.52	2.79
Brookfield, 70 cases. *c*	1886-1900.	9.73	12.61	.....	......	......	......	......	......
Brookfield, 84 cases. *a*	1886-1900.	11.68	15.13	17.7	25.0	26.0	19.6	11.2	7.2

a Figures compiled from the United States census.
b Figures obtained from "Statistics of Cancer in Massachusetts" by W. F. Whitney, M. D., published in the Thirty-second Annual Report of the State Board of Health of Massachusetts.
c Figures based on the 70 cases of cancer, as given in the Monthly Bulletin of the New York State Board of Health.
d Figures based on the 84 cases of cancer, as determined by my personal investigation.

TABLE V.—*Per cent of Cancer Deaths to Total Deaths, for All Ages and for All Ages over 30, for Brookfield Compared with New York State, United States Census Registration Area and New England States, with Ratios.*

	Brookfield.[a]	New York State.[b]	Brookfield.[a]	United States census registration area.[b]	Brookfield.[a]	New England States.[c]
All ages.......	9.73:3.42.	Ratio, 2.84:1.00	9.73:3.45.	Ratio, 2.82:1.00	9.73:3.53.	Ratio, 2.75:1.00
All ages over 30	12.61:6.04.	Ratio, 2.08:1.00	12.61:6.17.	Ratio, 2.04:1.00	12.61:6.25.	Ratio, 2.01:1.00

a Percentages based on 70 cases of cancer in period, 1886–1900, as given by the Monthly Bulletin of the New York State Board of Health.
b Percentages based on United States census for census year 1900.
c Percentages obtained from "Statistics of Cancer in Massachusetts," *loc. cit.*

TABLE VI.—*Certain Groups of Cancer Cases—Family Groups, "Cancer House" Groups, Husband and Wife Groups, Etc.**

GROUP I.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
1848..	Mrs. E. G	80	Hand ..	Mother.				
1850[1].	Mr. H. G	65	Face ...	Children.	Brother.	....	......	Two, same house.
1871[2].	Mrs. L. G. B...	80	Mouth..		Sister...	....	......	
1872[3].	Mrs. N. G. W..	70	Stomach		Sister...	....	......	
1882..	Mrs. S. G. B...	88	Face ...		Sister...	Mother.	......	
1891[4].	Mr. A. B.......	73	Face ...	......	....	Sons.	Brother.	
1892*a*.	Mr. M. E. B....	70	Stomach				Brother.	

[1] Lived in Utica, N. Y.
[2] Lived in Wisconsin.
[3] Lived in Utica, N. Y.
[4] Lived in Hamilton, N. Y.

GROUP II.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
1888*a*.	Mrs. P. S......	74	Axilla ..	Wife ...	....	....	......	Three, same house.
1893*a*.	Mr. P. S.......	76	Stomach	Husband	Brother...	....	......	
1884..	Mrs. M. J......	57	Stomach	....	Sister	....	......	
1898*a*[1]	Mr. W. S......	68	Stomach	....	Brother...	....	......	Two, same house.[1]
1900*a*[1]	Mrs. H. S......	67	Stomach	....	....	Niece ..	......	
1891*a*.	Miss P. L......	72	Mouth..	....	....	Aunt.		

[1] Mr. W. S. developed cancer in a certain house, but moved out of this house and died elsewhere one year later. Mrs. H. S. moved into this house directly after the death of Mr. W. S.; developed cancer in a few months and died in the house within eighteen months.

GROUP III.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
1850[1].	Mr. J. H.......	80	Face ...	Father.				
1850[2].	Mr. J. H., Jr...	60	Stomach	Children.	Brother.			
1880[1].	Mr. I. H.......	77	Face ...		Brother.			
1885[1].	Miss E. H......	86	Stomach		Sister.			
1892*a*.	Mr. G. W. H...	84	Stomach		Brother.			

[1] All three lived in different houses in Plainfield, N. Y.
[2] Died in Smyrna, N. Y.; developed cancer in Plainfield in a different house from the others.

* Each case that is included in the summary of 70 cases, for Brookfield, for the period, 1886–1900, is marked *a*. All cases, not marked to the contrary, died in different houses.

GROUP IV.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
1886*a*.	Mrs. S. N. A...	84	Stomach	Mother.				
1897*a*.	Mrs. H. M. C..	69	Stomach	Daug'ter	Wife.			
1894*a*.	Mr. H. M. C...	66	Stomach	....	Husband..	Brother.		
1896*a*.	Mr. J. A. C....	60	Stomach	....	....	Brother.		

GROUP V.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
1885..	Mrs. L. E. C...	66	Uterus .	Sister ..	....	....	......	Three, same house.
1897*a*	Mrs. L. E. B...	66	Stomach	Sister ..	....	....	......	
Living	Miss T. E......	..	Breast..	Sister ..	....	....	......	
....[1]	Mrs. E. C......	..	Colon ..	Sister.				

[1] Lived in North Litchfield, N. Y.

GROUP VI.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
1900*a*.	Mrs. S. F. B....	78	Liver...	Sister...	....	....	......	Two, same house.
1890*a*.	Mr. P. F.......	84	Face ...	Brother.	Father....	....	......	
1901[1].	Dr. A. D. F....	..	Lip	....	Son.			

[1] Had cancer of lip removed in 1891; died subsequently of apoplexy.

GROUP VII.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
.....[1]	Mrs. W. M.....	..	Breast..	Sister...	Aunts.			
.....[2]	Mrs. W. T.....	..	Uterus..	Sister...				
1897*a*.	Mrs. A. T. M...	49	Breast..	....	Niece.			

[1] Lived in Madison, N. Y.
[2] Lived in Sangerfield, N. Y.

GROUP VIII.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
.....[1]	Mr. A..........	..	....	Father				
.....[1]	Mr. A..........	..	....	Sons .	Brother.			
1887*a*.	Mr. B. J. A.....	53	Stomach		Brother.			

[1] Did not live in Brookfield.

GROUP IX.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
1866..	Mr. R. C.......	56	Lip	Father..	....	....	......	Two, same house.
1895*a*[1]	Mrs. F. C. P ...	54	Stomach	Daug'ter	....	....	......	

[1] Lived with her father until his death; subsequently lived eighteen years in Vermont; returned to her father's house in Brookfield in 1804 and within five months developed cancer.

GROUP X.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
1879..	Mrs. C.........	..	Uterus .	Mother ...	....	....	......	Two, same house.
1899*a*.	Mrs. M. C. B...	59	Uterus .	Daughter .	....	....	......	

GROUP XI.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
1894*a*[1]	Mrs. M. I. B...	35	Stomach	Wife	....	....	......	Two, same house.[2]
1896*a*.	Mr. M. I. B ...	43	Stomach	Husband .	....	....	......	

[1] There was a family history of cancer in Mrs. B's family.
[2] The house was new in 1889.

GROUP XII.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
1892a	Mr. P. W	63	Stomach	Not related	....	....	......	Two, same house.
1894[1].	Mr. H.........	..	Stomach	....	....	....	......	

[1] Mr. H. took Mr. W.'s blacksmith shop immediately after the latter's death and developed cancer within one year. He left Brookfield and died elsewhere. Nothing known of family history of either.

GROUP XIII.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
.... [1]	Mr. G. C......	..	Lip	Brother.				
1899a.	Mrs. R. C. R...	80	Stomach	Sister.				

[1] Lived in another county in New York. He had cancer of the lip removed in 1890 and died subsequently from another cause.

GROUP XIV.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
1888a.	Mr. A. A. B....	69	Stomach	Brother.				
1889[1].	Mrs. J. B. S....	..	Stomach	Sister.				

[1] Lived in Columbus, N. Y.

GROUP XV.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
1889a.	Mr. J. A. S.....	69	Face ...	Husba'd				
1897a[1]	Mrs. J. A. S....	67	Ovary ..	Wife ...				

[1] After husband's death, moved to another house.

GROUP XVI.

Year of death.	NAME.	Age.	Organ.	Relationship.				Remarks.
1899*a*.	Mr. T. P.......	77	Liver ..	Brother.				
1899*a*.	Mr. J. P.......	85	Hand ..	Brother.				

TABLE VII.—*Cancer Houses—Multiple Cases of Cancer Occurring in the Same Houses in Brookfield, Classified with Reference to Consanguinity and to Family History of Cancer.*

- "Cancer Houses". 9
  - Two cancer cases each.. 7
    - Cases related by blood............ 4
    - Cases not related by blood........ 3
      - Family history cancer, both sides.......... 1
      - Family history cancer, one side only...... 1
      - No family history cancer............... 1
  - Three cancer cases each.. 2
    - All three related by blood........ 1
    - Two related by blood, the third not related...... 1

February 1, 1903.

A CANCER DISTRICT IN THE TOWNS OF PLAINFIELD AND EDMESTON, NEW YORK.

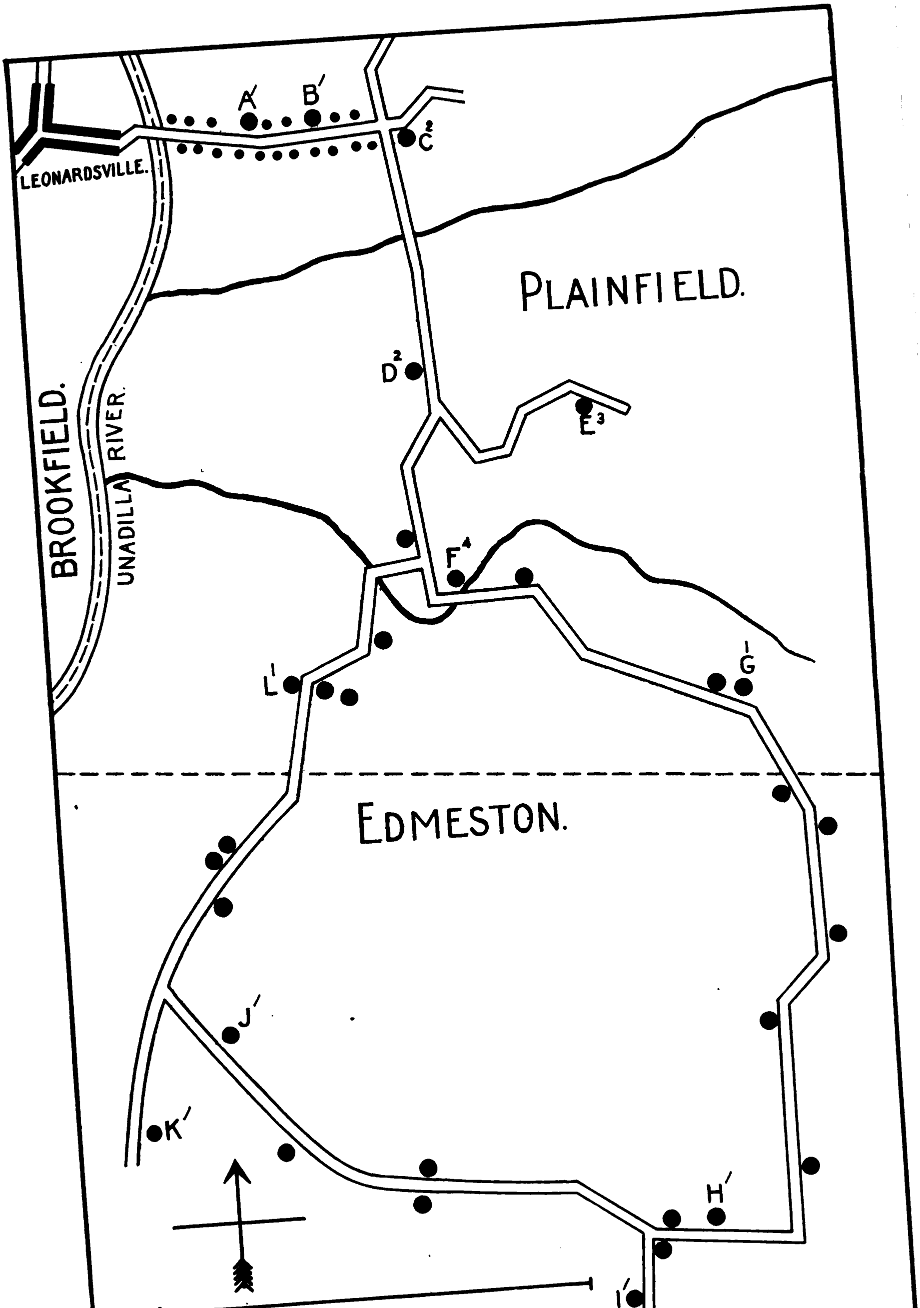
By Irving Phillips Lyon, M. D.

While engaged in studying the cancer distribution in the town of Brookfield, my attention was drawn by certain physicians to the fact that quite a cancer focus had previously existed just across the town line of Brookfield in the towns of Plainfield and Edmeston, Otsego county, and in consequence I made an investigation of the subject on the spot.

The area embraced in this cancer district is about 2.5 x 1.5 miles, in a rough, hilly farming country. The accompanying road map shows the location of every house in this district, indicated by black dots for houses in which no cases of cancer have occurred within the recollection of the older physicians and inhabitants, and by red dots for cancer houses. Each cancer house is further marked on the map for the number of cancer cases known to have developed in it, and is given a letter for the purpose of reference.

It will be seen that this map shows twelve cancer houses, including nineteen cases of cancer, in the limited territory represented—a much greater number than known in other districts of similar size and population in the neighboring country. The dates of death of these cases (Table I) indicate that cancer occurred more frequently years ago than recently. Thus 10 of the nineteen cases were before 1875 and 15 before 1885, only four having occurred in the period 1885-1900. It will be noticed also that the ages at death were generally quite advanced.

I made a rather careful inquiry into the family histories of the persons who had developed cancer in these houses and found, as given in detail in Table I, only four cases among the nineteen that failed to have a positive history of cancer in other members of their


LEONARDSVILLE.
A′
B′
C²
PLAINFIELD.
D²
E³
F⁴
BROOKFIELD.
UNADILLA RIVER.
G′
L′
EDMESTON.
J′
K′
H′
I′
SCALE: 1 MILE.

families, and of three of these four cases little or nothing as to family history could be ascertained. In view therefore of the great preponderance of a further family history of cancer among these cancer-house cases, I am of the opinion that *this cancer district represents a concentration of cancer families rather than cancer houses.* For the benefit of those who deny the influence of heredity in determining the development of cancer in families, I would make the same reservations and suggestions indicated in the preceding report on the cancer mortality of Brookfield.

In conclusion I desire to acknowledge my indebtedness to Dr. O. L. Southworth of Plainfield for much assistance in working out the details of this cancer district.

TABLE I.—*Relation Between Cancer Cases in "Cancer Houses," Consanguinity and Family History of Cancer.*

Year of death.	NAME.	Age.	Organ.	House.	Relationship.				Remarks.
1868....	Mr. S. D	70	Stomach ..	E	Husband ...	Brother.....	Uncles ...	Granduncles.	
1869....	Mrs. S. D	68	Stomach ..	E	Wife.				
1884....	Mr. J. D	91	Stomach ..	L	....	Brother.....			
1882....	Mrs. S. D. T....	55	Stomach ..	H	Cousin	....	Nieces.		
1887....	Mrs. H. E. McI.	53	Abdomen .	..	Cousin	....			
1891....	Mrs. S. D	55	Breast	J	Mother.				
1899....	Dr. E. D	40	Face ...	Another town	Son	....	....	Grandnep'w.	
1884....	Mrs. J. T.......	77	Breast	E	Not related..	....	....	....	No family history of cancer.
1850....	Mr. J. H., Sr...	80	Face	G	Father.				
1870....	Mr. J. H., Jr...	60	Stomach ..	D	....	....	....	....	Developed cancer in Plainfield, died in Smyrna, N. Y.
1880....	Mr. I. H	77	Face	..	Children.				
1885....	Miss E. H......	86	Stomach ..	..					
1892....	Mr. G. W. H ...	84	Stomach ..	Brookfield					
1861....	Mr. W	85	Face	F	Husband ...	Parents.			
1870....	Mrs. W	95	Uterus ...	F	Wife				
1873....	Mr. J B. W	80	Stomach ..	F	....	Children.			
1892....	Miss S. W......	85	Face	F	....				
1862....	Mr. H. C.......	Old	Stomach ..	D	Father.				
1890....	Mr. G. C.......	68	Lip	Another town	Children.				
1899....	Mrs. R. C. R....	80	Stomach ..	Brookfield					

1855....	Mr. S. W........	60	....	....	Father.				Father and son lived one mile apart; cousins' fathers were brothers.
1896....	Mr. H. J. W....	66	Stomach ..	B	Son	Cousin.			
1889....	Mrs. L. A. C....	47	Stomach ..	....	....	Cousin.			
1835....	Mr. J. C.......	64	Rectum...	C	Father.				Mr. J. C. and Mrs. C. H. C. W. died in different houses built on exactly the same spot.
1877....	Mr. F. C.........	61	Stomach ..	A	Children.				
1884....	Mrs. C. H. C...	75	Uterus ...	C	Children.				
1860....	Mrs. D. W.....	50	Stomach ..	K	Sister.				
1868....	Mrs. H. W.....	65	Breast	Brookfield	Sister.				
1895....	Mrs. I. T.......	74	Uterus ...	I					Family history of cancer.

February 1, 1903.

A REPORT UPON THE PHYSICS AND THERAPEUTIC VALUE OF KATHODE AND ULTRA-VIOLET RAYS, WITH REFERENCES TO THE ELECTRO-MAGNETIC THEORY OF LIGHT.

An Attempt to More Clearly Define the General Character of These Recently Introduced Agents in the Treatment of Cancer.

By Roswell Park, M. D., LL. D.

Within the past eighteen months there has been such general interest aroused in the treatment of certain cancerous and other infectious diseases by kathode and ultra-violet rays, and so many have been induced to experiment therewith that it has seemed to me wise to study more carefully the nature of these agents in order that we may more fully comprehend their physical characteristics before employing them too indiscriminately.

It is very certain that but a small proportion of the physicians who are purchasing more or less expensive appliances, to whose uncertain effects they are subjecting their patients empirically and often rashly, have an adequate comprehension of what they are doing or how doing it. This report is a brief epitome then of recent researches into the physics of certain widespread or universal phenomena with which, it seems to the writer, all should be acquainted who purpose taking up and practising the so-called X-ray or Finsen light treatment of cancer. It is not intended to present here directions for their use, nor to report cases, though to give it a certain "practical" character a few conclusions are appended. *It is too early yet to report cases.* Considerable time must yet elapse before we can speak with certainty as to the actual value of these new methods. Mean-

time, while waiting for these results, we can accumulate experience and we can broaden our acquaintance with the agents to which we are resorting. It is hoped that this report will be of assistance in this direction. The subject is approached, as will be seen, with this purpose distinctly in view.

Periodically in the history of events, and in the advance which science is constantly making, it has become necessary to not only stop and as it were take account of stock, but to entirely revise present notions; sometimes in accord with entirely newly discovered facts, at other times in accord with older and perhaps abandoned views. This is true at the present time with regard to the most elementary notions concerning the physical character of light and electricity.

The primary concepts of science have included the existence of matter in an incomprehensibly minute division, each tiny particle being spoken of as an atom. Some such concept was absolutely necessary for purpose of measurement and calculation and as a basis upon which to build a superstructure. While no one ever has seen, and probably no one ever will see an atom, nevertheless the existence of atoms has been universally conceded by all scientists as a necessary postulate of thought and computation. Scientists have even gone so far as to calculate the size of the atoms, and Lord Kelvin figures the average atom as one twenty-five millionth of an inch in diameter. This is not merely the scientific use of the imagination, as Tyndall used to say, but is based upon calculations which have very much to support them and practically nothing to weaken them save the lack of power of our finite minds to comprehend the infinitely small. But the existence of atoms of this size as a postulate of physical science does not supply the demands now made upon it, and of late men have been seeking a demonstration of the existence of particles still smaller by whose activity and ceaseless energy certain natural phenomena may be explained. Both the size and the activity of these ultimate particles transcends the limits of our imagination, yet they are necessary adjuncts to such conceptions of them as we can form. The ordinary conception of an atom has been that in one cubic centimeter of gas there are twenty million, million, million

($2x10^{10}$) molecules. This was Loschmidt's estimate, and it has been confirmed independently in several ways, among others by the electrolytic method and by Lord Rayleigh's calculations concerning the opacity of the air.

The researches of Prof. J. J. Thompson, assisted by those of Sir George Stokes and Professor Townsend, have now apparently established the existence of particles not larger than one-thousandth of the diameter of the atom whose size has just been stated, each of which is capable of carrying a tiny charge of negative or positive electricity; those carrying negative charges being those which most interest us here. It is a stream of these proceeding from the kathode which causes the Roentgen ray, instead of light rays vibrating in a lateral instead of a longitudinal direction, as was at first held. It will be seen that this is not far from accepting Crooke's fourth or radiant state of matter. The greenish phosphorescence of a Crooke's tube is due to the bombardment of the attenuated gas which it still contains by this stream of particles, which are now usually spoken of as *corpuscles.* Although it was at first held that this stream could not be deflected nor reflected, it is nevertheless true that it may be, at least in part, deflected by an electrostatic or magnetic field, if only the vacuum be high enough.

These corpuscles are also given off by incandescent metal, by cold metal when illuminated by the ultra-violet ray, and by radium. Everywhere when pressure of gas is relatively low, i. e., when there is a vacuum, and when the corpuscles find few atoms to which to adhere and give up their electric charges, it is found that they are the carriers of negative electricity.

Thompson has recently shown (Popular Science Monthly, August 19, 1901) that there is a remarkable difference between negative and positive electricity, for the latter instead of being associated with a constant mass (i. e. corpuscles) one-thousandth the size of a hydrogen atom, is connected with a mass of the same order as an ordinary molecule, varying of course with the gas in which electrification takes place. That is, the carriers of negative electricity are infinitesimally minute and invariable, while all the positive masses are larger and quite variable. This naturally suggests a view that these corpuscles

themselves, or ions, constitute negative electricity and that positive electricity simply implies their absence from ordinary atoms. This takes us back to the old Franklinic view, that electricity comprised a fluid, and makes us think that in using the term electric fluid they were wiser than they knew, and that changes in the state of electrification are due to transportation from one place to another. It seems to be established that a body negatively electrified has its volume augmented, while positive electrification involving absence of corpuscles is accompanied by diminution of volume. Thus a charged body by virtue of its charge possesses proper mass apart from the ordinary matter composing it. All of which Thompson showed twenty years ago.

These corpuscles are not the atoms of a metal but infinitely smaller bodies which are the same for all substances. Their failure to escape from a metal, or from the surrounding air or medium, is due to the fact that negative corpuscles are attracted by positive atoms, even by neutral, hence the fact that metals, especially some of them, are such great conductors. Under the influence of great heat or of the ultra-violet rays, the corpuscles seem to acquire enough energy to escape. Radium constitutes an exception to this statement since emanation or escape from it takes place as rapidly as 2×10^{10} times per second, or two-thirds as rapidly as light moves, while they have a very much more penetrating power. Since gas becomes a conductor when the corpuscles pass through it, but not when its pressure is reduced, we have an explanation of electrical phenomena occuring in our upper atmosphere, especially when its density and movements are controlled by such currents as are known to occur. Variations in the earth's magnetic field, and consequently in the compass, may thus be explained. The conception and acceptance of those views about corpuscles, which I have just summarized, have necessitated a complete revision of previous opinions. These corpuscles, considered to be not larger than one-thousandth of the size of hydrogen atoms, each bearing its charge of negative electricity, are known to be discharged with tremendous velocity:

1. From the negative electrode in a Crooke's tube, kathode rays.
2. From objects impinged upon by these kathode rays (X-rays).

3. From exceedingly hot bodies such as incandescent metals.
4. From cold metals under the influence of the ultra-violet rays.
5. From the radio-active substance or element radium.

These corpuscles, or ions, passing through a gas produce other ions by collision with its molecules. These ions also with their peculiar electric properties serve as nuclei for the condensation of ordinary matter. It has been the particular service which the great Sweedish physicist Arrhenius has rendered, that he has introduced this conception of the electro-magnetic properties of these ions into the theory of light, and has shown that while the ordinary properties of light may be considered as still amenable to the so-called laws under which they have so long been studied and classified, there still needs to be introduced into the subject this entirely new feature by which, along with the wave motion to which we have been so long accustomed, certain other physical features must be added.

Kepler and Newton, who regarded light as a corpuscular emanation, would perhaps appear to have considered it more wisely than they then realized. The hypothesis which they built up was superseded by the wave theory of Huygen's, upon which until very recently all optical calculations were made. It does not disturb the practical value of these calculations if we assume that there is actual projection of matter in the direction of the light waves;—matter probably of this corpuscular and elementary character which has the power of permeating space and all other material out of which the elements are probably built up, and which travels with simply inconceivable rapidity.

Let us now step aside for a moment from the consideration of therapeutics to see how well these views of Arrhenius fit the various facts regarding the nature of certain universal phenomena, since if our primary concepts can be shown to be comprehensive and correct, it helps very much in limiting the field of inquiry to so relatively small a proportion as that of the therapeutic value of certain light rays. It is known that the surface of the sun evinces a wonderful repulsive force, which at least until now could never be satisfactorily accounted for. Aside from its heat-giving power, it is our principal

source of emission of light. Until recently it had not been generally suspected that a ray of light could exert the faintest pressure, although Maxwell calculated in 1873 that sunlight at the earth's surface should exert a pressure of .6 x 10 to the minus tenth power in grams on every square centimeter ($.592 \times 10^{10}$). Arrhenius, practically accepting this calculation, has shown that on the sun's surface this pressure amounts to 2.75 mg. for every square centimeter. If now one gram of water (i.e., 1 c.c.) weighing this amount at the earth's surface, could be carried to the sun's surface and weighed there; it would be found to weigh 27.5 grams; that is, the attraction of the sun would draw it in with 10,000 times the force with which the sun's light would tend to repulse it. But now if instead of a cubic centimeter, we consider a much smaller cube the pressure on its base would diminish as the square of its edge, but its weight would diminish as its cube or volume. Consequently there must come a point when the pressure of light would balance the weight of an exceedingly small particle and finally exceed it. That is, as Cox has described it, these particles would behave as if gravity had become negative or reversed. This limit in minute size is approximately reached with a cube whose edge is one mikron in length; that is, one-thousandth of one milimeter.

Here we face this apparent paradox, that providing particles are small enough the pressure of light may be a much more active factor in their activities than their weight. This will explain, for instance, the long time required for the settling of very small particles in the air, and thus we may account for the red sunsets which were noted for so many months following the eruption of Krakatoa.

But nothing will so illustrate the terrific pressure and repulsive force to which these particles may be subjected as the motions, and especially the curvatures, of comets' tails, where the repellant force equals or far exceeds the gravitational or attractional force of the sun. Arrhenius and Bredichin have gone even so far as to calculate the size of the particles in the tails of certain comets, basing their calculations on the hypothesis that as comets approach the sun its intense heat provokes a violent eruption of hydro-carbon vapors, especially on its exposed side; that as the hydrogen boils

off the vapors condense into minute drops or particles, of which the larger may drop back while the smaller are driven off from the sun, forming the comets' tails which have been so often seen pointing away from it. They calculate also that particles thus driven may traverse a space equal to the sun's diameter (850,000 miles) in a few minutes. If this be true the formation of tails 120,000,000 million miles long within two days, as has been actually seen, is shown to be theoretically possible.*

Equally well are the phenomena of the corona and smaller prominences accounted for. The sun must project enormous quantities of vapor into space. If this vapor condenses into particles larger than the critical size above referred to (i. e. so that their weight prevents their projection by light) then they fall back toward the sun, giving rise to the prominences seen during total eclipses; if smaller they are driven into space to enormous distances, and appear as the streamers of the corona. Particles of just the critical size may float in clouds such as are also observed.

The zodiacal light may also be explained by the streams of electrically charged corpuscles which the sun emits, which by the time they reach the higher and rarified regions of his own atmosphere are practically Roentgen or kathode rays. If very hot metal emits these rays, as we know it does, there is every reason to think that the superheated sun's surface does the same. Those rays which are visible to us lie mostly in the plane of the ecliptic, and give rise to the peculiar evening glow in the west which we speak of as the zodiacal light. This will also explain that similar but very faint

*At a recent meeting of the American Physical Society in Washington (Dec., 1902) Nichols and Hull described an experiment by which something greatly resembling a comet's tail was obtained under conditions approximating those of nature. A powder consisting of a mixture of emery and puff-ball spores was placed in a vacuum tube constructed somewhat like an hour-glass. The vacuum was made as perfect as could be obtained, precautions being also used to get rid of mercury vapor. Upon pouring the powder from one part of the tube to the other, and at the same time concentrating upon it the rays from an arc, the lighter portions of the powder were seen to be blown out as though repelled by the light, and presented an appearance quite similar to that of a comet's tail. The effect was of the same order of magnitude as would be expected from the author's values for light pressure.—*Science,* Jan. 30, 1903, p. 181.

appearance sometimes seen before the eastern sunrise which the Germans have significantly termed the "gegenschein."

No one can have watched the aurora without being struck by the similarity of its manifestations to those of the kathode rays in a Crooke's tube, especially when these latter are subjected to a magnetic field when they describe helices about the lines of force. The negative particles coming from the sun are scattered most thickly on the equatorial regions of the earth which are most exposed, but before they reach a level in our atmosphere dense enough to excite luminescence they are caught in the lines of force of the earth's great magnetic field and follow them. As these lines dip outward from the equatorial heights toward the surface, at our magnetic poles, they finally reach an elevation where the rarefaction is comparable with the vacuum of a Crooke's tube, and here they begin to give out the shifting, darting lines of enormous kathode rays. When they reach the denser layers of the air their energy is exhausted, hence the dark circles around the magnetic poles from which they seem to dart. The Swedish North Pole Expedition, by a large number of trigonometrical observations, established that the average distance above the ground of the base of the aurora is, at Spitzbergen, about 34 miles, at which height the pressure of the atmospheric nitrogen is about one-tenth of one millimeter. It has been also shown that at such pressures the rays of nitrogen and oxygen fade, while those of argon and the other light elements, helium, neon, krypton and xenon take their place. Furthermore, that electrical discharges traverse six or eight times as much space in helium and neon as in hydrogen or argon. This will also explain why the spectra of argon and neon are seen in the aurora much oftener than those of helium, krypton and xenon.*

Additional plausibility is given to this explanation by the relation now universally accepted between sun spots, auroræ and magnetic storms, which have a common variability.

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*Air contains by volume, at the earth's surface;

1% argon.

1 or 2 parts neon per 100,000.

1 or 2 parts helium per 1,000,000.

1 or 2 parts krypton per 1,000,000.

1 or 2 parts xenon per 20,000,000.

If kathode rays really occur in this way and to this magnificent extent, our aurora being occasionally visible evidence thereof, then the negative ions formed by ionization of the air will form centers for condensation, and falling to the earth will charge it negatively, leaving the air at moderate heights charged positively. If this be true then clouds should be more common in years when the aurora is more frequent, which is actually the case, since condensation will depend upon the number of ions available for nuclei. The ordinary phenomena of lightning are then to be interpreted as immense sparks taking place across this spark gap.

This theory is capable of further extension to cover the formation of meteorites and nebulæ. By the aggregation of those particles which miss the earth and the planets larger masses are formed, or by the union perhaps of these with similar streams proceeding from other suns. Thus are constructed masses of various size which obey gravitational impulses, or the attraction of other masses, and move in space in accordance with these governing impulses. Yet other particles escape the other suns and stars and help to form the gaseous nebulæ, for it is well known that there are certain nebulæ which are not resolved by any telescope and whose constituents are shown by the spectroscope to be gaseous. These exist in interstellar space at the temperature of absolute zero, at which molecular activity is almost or quite stilled and are not capable of shining by any property of their own. Only their outer borders shine because of their bombardment by these particles which give up their electric charges and cause the gases of the nebulæ to shine like those of a vacuum tube.

Such is a very brief résumé of the electro-magnetic theory of light as comprised in the fascinating and ingenious speculation of Arrhenius, as popularly set forth by Cox (Popular Science Monthly, January 19, 1902, p. 265), and may perhaps serve to give a little clearer notion as to the so-called corpuscular nature of both electricity and light.

We are now so accustomed to availing ourselves of that most interesting fact discovered by Roentgen only seven years ago—that the kathode rays of a Crooke's tube not only produce fluorescence of

certain salts, but permeate many apparently solid objects while causing others to cast shadows—that we are inclined to forget how recent is this discovery, and how much it has meant to us. We are also likely to forget that Roentgen was but the last one of a group of men who had been studying the phenomena of electrical discharges in vacua. Crooke succeeded in producing higher vacua in sealed tubes than any of his predecessors, and he had reduced the pressure of the residual air in these tubes to about one ten-millionth of an atmosphere. He had shown also that at a certain stage of this exhaustion electric discharges from the kathode became visible, and had assumed that this was a projection of active matter shot off from the negative pole with a velocity which he figured at about 250,000 yards a second. Lenard in 1894 found that these rays traveled better in a vacuum than in air, that they would pass through substances opaque to ordinary light and affect a photographic plate. It was Roentgen's service to show that when the degree of vacuum was increased a variety of rays was given off which were more powerful than the Lenard rays, which seemed to be unaffected by the magnetic field, and that particularly those salts which are now used in the fluoroscope glowed under their influence.

The nature of the kathode rays is not now quite as mysterious as it was when they were first discovered. To more completely understand them we should refer to the ordinary spectrum thrown upon a screen when light passes through a prism. The more we extend our knowledge of this spectrum the better we appreciate that beyond the red end may be felt the heat waves, which are of longer wave length and which do not pass so easily through glass as does red light; thereby affording the reason for the use of a glass fire screen. Beyond these rays are others of still longer wave length which were carefully studied by Hertz and are often known as the Hertzian rays, which have the peculiar property of converting poor electrical contacts into good ones when they fall upon them. A demonstration of such effect may be made with powdered aluminum which ordinarily is a poor conductor, but which under the influence of Hertzian rays becomes a good one. These rays are supposed to have wave lengths even several miles in length, and they are the

longest in this respect of any that have yet been discovered in the spectrum. Proceeding from this ultra red end toward the other end of the spectrum we find that wave lengths rapidly diminish, and when we come to those known as the ultra violet they are estimated as only one sixty-thousandth of an inch in length. These ultra-violet rays are also ordinarily invisible but can be demonstrated by their property of producing fluorescence in certain substances, for instance uranium glass, which under their influence shines with a greenish yellow light. They also affect the silver salts more speedily than do the visible rays of the spectrum.

Beyond the region of these actinic rays are others, called after Niewenglowski and Becquerel, who discovered them.

The phenomenon of phosphorescence is as yet one of nature's mysteries. It has long been known that calcium sulphide, which is the basis of luminous paint, shines in the dark,—but only after it has been exposed to sunlight; by such exposure it has acquired a property it loses after a time.

Niewenglowski was probably the first to establish the fact that from phosphorescent substances certain luminous rays are emitted which may pass through opaque screens and affect sensitive plates. He proved this with calcium sulphide which had been thus exposed to sunlight. It emitted rays which passed through an aluminum plate. But Niewenglowski's rays are due to the action of sunlight upon the material which he used and which later emits them. Without preceding sunlight there would be no rays of this character. And these rays are refracted by glass like ordinary light rays, this apparently showing that they are not made up of a stream of corpuscles as are the kathode rays. These rays were first studied by Becquerel and may be spoken of as Becquerel's rays; i. e., light rays of ordinary wave motion capable of penetrating certain opaque objects.

Becquerel very early conceived the idea of studying whether the property of emitting powerfully penetrating rays was not intimately bound up with phosphorescence. He proceeded empirically by placing various phosphorescent substances enveloped in opaque wrappings upon sensitive plates. In this way he discovered that a mineral containing the metal uranium left its marks upon the plate,

and that it was not necessary that this material should be previously exposed to sunlight. By further ingenious experiments it was shown that uranium in metalic form, prepared in the electric furnace, gave out greater abundance of rays than did any of its compounds, and that this emission of rays was continuous and direct, even, so far as could be seen, never ceasing. The next step was to ascertain whether this property was due to uranium itself or to some other substance contained within it. A further study showed that the metal contained certain impurities, and further still that these impurities were composed of at least three distinct elements—radium, actinium and polonium. Uranium is prepared from pitchblende. From this mineral Professor Curie and his wife isolated a very small quantity of radium which they finally got in a nearly pure form of radium chloride, which has been shown to have a ray emitting power several hundred thousand times greater than uranium. If radium could be secured in pure form it would have a value of nearly $1,000 a grain. To-day in all the world there is less than a gram of pure radium chloride, and the other elements mentioned are mainly known by their spectra.

Becquerel rays then are these emitted by radium in some of its forms. Radium stands alone, so far as is at present known, in its powers in this direction. If a tube of its chloride be held to the forehead in the dark, with closed eye, the experimenter will still see light, since the retina itself becomes phosphorescent. It shines quite vividly by its own light. When applied in sealed tubes to the outside of the body it produces intense dermatitis, or even sloughing of the skin. It imparts its radio-activity to any substance placed in its neighborhood. Not only metal objects but the clothing, and even the bodies of exposed experimenters, give out rays capable of affecting photographic plates and discharging electroscopes.

It has been lately proposed to employ radium locally over superficial cancers, and to thus take advantage of its wonderful properties in influencing the disease process. But until it can be procured in some reliable or semireliable form this will be impossible. A gram, if it could be procured, would be worth at least $10,000 to-day, and there does not exist at present in all the laboratories of the world even so much of this precious substance.

Becquerel further experimented as to the effect of a magnet upon these rays. He has shown that some of them at least are deviable while others are not; that is, they really consist of two distinct kinds of radiation, one influenced, the other uninfluenced by the magnet. The former seem to be identical with the kathode rays of a Crooke's tube, while the latter are identical with those particularly described by Roentgen.

Perhaps the greatest mystery of all is the source of the ceaseless energy which radium emits. The answer will probably be found in those vibrations of ultimate matter which are transmitted throughout space, which as Duncan has said is all aquiver with the waves of radiant energy, ranging from the infinitely short to the incomprehensibly long, the rays which most interest us being exceedingly short, while the waves of great length, corresponding to the sound waves of the organ diapason, are the waves of Hertz and Marconi, equally mysterious but concerning us less at this time and place.

It is known that certain insects and small animals give off a peculiar radiation which much resembles the Niewenglowski rays, which will pass through aluminum and affect sensitive plates. Finally, still further along in the scale, we come to the kathode rays, for which our only source at present seems to be electrical discharges in high vacua. These rays have a wave length and a velocity which can scarcely be measured. I will not attempt here to state the figures. They are doubtless of the same general character as those manifestations seen high in our atmosphere, which occur at any or all times but which are more visible at night, to which we give the name of the aurora. There is every reason to think that both are produced alike by a stream of the corpuscles of which I spoke in the early part of this paper, or of that incomprehensibly attenuated matter to which in times past we have vaguely given the name ether, and to which Crooke referred in his description of the fourth or radiant state of matter.

When these discharges occur under our control and production it may be noted that the kathode rays will not only cause fluorescence and affect sensitized plates, but that they also will discharge bodies charged with electricity, their powers in this direction being more conspicuous than those of the ultra-violet rays. The reason for

this last fact is that the kathode rays destroy for the moment the insulating properties of the air, and that the electricity consequently leaks away from the charged body. Apparently they do not show this effect through solid insulating material, nor even through the skin.

So far as the action of the X-rays upon micro-organisms is concerned numerous experimenters have reported various results, some of which are quite contradictory. Experiments have been made in various ways, with bouillon and plate cultures manipulated in various ways, and the organisms experimented with have been of all degrees of virulence. Perhaps the most instructive of these were made by Reeder, who exposed culture plates beneath sheets of lead with openings made in them so arranged that the rays would fall upon distinct portions of the culture further on, even excluding ordinary light by black paper. He found that the various organisms flourished in those parts where they were sheltered from the X-rays by the relatively opaque lead screen, whereas on the exposed areas they were either absent or feebly developed. That the chemical nature of the medium was not altered was shown by the fact that cultures subsequently grew upon these areas. These experiments are certainly suggestive and indicate the probability of inhibition of bacterial growth by X-rays, or else by electrical influences in connection with them, to which influences alike would be exposed those parts of the body which are subjected to the X-ray treatment of to-day.

The general conclusion which Reeder reached is, that bacteria outside of the body, in suitable media, can be deprived in this way of capacity for further development.

A number of experimenters have carried these investigations further, and after inoculating animals with various bacteria have exposed them to the X-rays. These results have been practically negative.

Passing now from electricity to light we must study it first by some of its effects. Our knowledge concerning the action of light upon living organism, animal or vegetable, is very inexact. It is known that the rays of the darker end of the spectrum, namely the most refracted, are those possessing the greatest degree of chemical

and the least degree of heat activity. The reason for this is absolutely unknown. Studies on the effect of monochromatic light would seem to indicate that upon animal organisms the chemical rays seem to exercise something of a distinct influence.

That plants are very easily influenced by light has been firmly impressed upon my mind ever since I saw the late George Romanes demonstrate before the British Physiological Society, in 1890, experiments which he had made with fresh and tender young mustard plants. He sowed the seed in suitable small receptacles and when it began to sprout placed them in a dark chamber. In this chamber electric sparks were produced by an induction coil at varying rates. Invariably the plants turned their tops in the direction of the sparks even when these were produced so slowly as once a minute. It was as though every tiny plant were looking toward the source of the light. I have never seen these experiments of Romanes referred to, but it seems to me that they have an importance of their own.

This appears corroborated by this fact: The ultra-violet rays have the property of discharging a negatively electrified body. When such a body be provided with a zinc surface it has been shown that while the rays produced by an arc light required 12 seconds to discharge an electroscope the condenser spark would do the same thing in 5 seconds. Evidently then condenser sparks are very rich in ultra-violet rays. (Turner, Medical Electricity, p. 365.)

The effect of ordinary light upon bacteria has been studied by many observers, who generally agree upon the conclusion that light is of itself the best, cheapest and most generally available of bactericidal agents. Experiments with monochromatic light have shown individual differences, and it would appear that the heat rays are much less effective than the chemical rays. Gruber has shown that the violet rays have a much more pronounced effect upon ordinary earthworms than do the red rays, and that this effect is perceptible even upon decapitated worms. Dubois has made similar experiments with proteus, which is the most active in the darkness of the red rays and least so under the influence of the chemical. Fifty years ago the Vienna physiologist Bruecke demonstrated the color scale through which the chameleon would pass on changing from darkness to light, which changes are due to the pigment cells

in the skin, and which he showed to be thus capable of migrating from the depths to the surface and vice versa. Paul Bert carried the experiment further and exposed one-half of the chameleon's body to red light and the other part to blue; under the former the skin remained light, under the latter it changed to dark. Numerous other experiments made upon animals would indicate the role played by light in their pigmentation.

So far as the human skin is concerned it is of course possible to very seriously affect it by heat rays, but it would appear that under ordinary circumstances it is the ultra-violet or chemical rays which produce both pigmentation and erythema, the latter often extending into a dermatitis.

The same effects are produced by sunlight in the polar region as in the tropics. It was Charcot who in 1859 first stated that the chemical and not the heat rays of electric lights produced skin affections identical with those produced by sunlight.

It would appear, furthermore, that the pigment in the skin serves as a protection against the chemical rays, which fact was perhaps first stated by Unna in 1885. In general we know that as we approach the equator we find mankind darker in color, and that the most gorgeous plumages are found in tropical regions. Moreover, the most exposed parts of the body seem to be thus most protected by pigment. The back is usually darker than the belly, and this is conspicuously so in the case of creeping animals and flat fish. Sunlight seems to have the same effect also upon vegetation, the degree of coloration depending not upon the intensity of the light but upon the number of chemical rays.

The irritative action of the actinic rays upon the skin may produce all sorts of lesions, from the mildest hue to a gangrenous destruction, depending not alone on the intensity of the light but the proportion of its chemical rays. These lesions are naturally more pronounced upon persons of light complexion or blondes, while albinos suffer most. Observers have studied the effect of electric light upon the skin and eyes. Maklakow in order to protect others studied the effect upon himself and suffered severely both in his eyes and upon the skin of the face, the pain and œdema of

the face and conjunctiva being almost unendurable. Widmark, examining the subject for himself, found that when the ultra-violet rays were excluded the skin was uninjured, when the heat rays were excluded there was no particular difference.

In this connection there enters another factor, apparently unappreciated until Finsen and his pupils took it up. It relates in fact to this, that only such amount of light as is actually absorbed by the tissues is of injury to them. In other words, the actinic effect of light is directly proportionate to the degree of its absorption. When now we test tissues to see which has the greatest capacity of absorption we find that in reality the blood excels in this respect. This is a matter to be again alluded to, but it affords the explanation for the practical demonstration of the fact that the parts to be exposed to the Finsen light are to be made as bloodless as possible. Exposure to light is again the explanation for not a few of the pigmentary and other lesions of the skin, e. g. pellagra and xeroderma pigmentosum or melanosis lenticularis. The first appearances are met with upon those parts most exposed to light.

Again, the influence of light upon the course of variola seems to have been recognized for a good many years. It was first mentioned in 1832 by Picton and in 1867 and later by Black, Barlow and Waters. One will readily recall that the deepest and most numerous scars occur upon the face and hands. Finsen and numerous other observers have noticed that by keeping smallpox patients in rooms with red glass windows, similar to the dark rooms of the photographer, i. e., that by thus filtering out the ultra-violet rays, there was very much less tendency to markings on the skin. Finsen also calls attention to the fact that it is possible to more or less protect the skin from the infection of the chemical rays by painting it with tincture of iodine, or with solution of copper sulphate, or with some ointment. The iodine colors the skin yellow; the copper solution absorbs the actinic rays and tends to color the skin black, whereby all rays are kept out.

In this connection it is worth while to remember the fact alluded to by Petersen, that in the middle ages it was customary to treat smallpox with a red colored environment, since red bedding was used, red balls were placed inside the bed, etc. Exactly what the

results were we do not know. In Roumania there used to be an ancient custom to cover the face and hands of smallpox patients with red cloth, and a French naval surgeon wrote sometime ago that he had often seen in Tonkin these patients shut up in alcoves which were completely closed with red hangings.

At all events it would appear that the exclusion of chemical rays should be *absolute;* that it should be continuous until the vesicles are completely dried up; that even a short exposure to light materially damages the result; that the treatment should be begun very early; that it in no wise interferes with any other treatment, and that by resorting to it suppuration and disfiguration can be remarkably diminished in degree and extent if not absolutely prevented.

Finsen has also carried out a number of interesting observations upon the irritating properties of chemical rays. For instance, very young salamanders lying at the bottom of a dish of water are not disturbed by red or yellow light, but by blue they were promptly excited to movement; so it was too, as before remarked, with the ordinary earthworms which would collect beneath the red and avoid the blue glass. Gruber had also the same results, from which it would appear that various animals can distinguish by their integuments between red and blue; while they seem to enjoy the former, they avoid the latter tint. He found this true to such an extent that he described a specific photo-dermatic sense. The same thing may be seen even with common house flies. Indeed the effect may be so pronounced as in certain cases to produce reflex motions in embryos and lively reaction in various smaller animals. It thus would appear that light is awakening in more than one sense.

Nearly all investigators having agreed that light is a powerful bactericidal agent, it is not strange that certain infectious diseases of the surface of the body, when exposed to it, have been found to yield to the treatment. In fact, at present it seems to be a question merely of the depth to which its effects may be made to be felt. There is no better illustration of a lesion of this kind than ordinary lupus. There is no question but what sunlight would be always the most serviceable for this or similar purposes were it always available. When it can be used a very simple chambered plano-convex lens,

can be used for the purpose. It should be several inches in diameter, with chamber open at the top in order to permit it to be filled with a methyl blue or blue vitriol solution, by which the heat rays are filtered out. This only needs to be mounted as is a compass in order to permit of its use whenever the sun is shining brightly.

I have already remarked upon the light absorbing powers of the blood. A very simple experiment may be tried at any time which will show the necessity for rendering the parts exposed to phototherapy as bloodless as possible. A piece of sensitive albumen film may be placed behind the ear in contact with the cartilage. If now the ear be exposed to ultra-violet rays, even for several minutes, without compression, the effect upon the film is relatively small, but if the cartilage and the paper be pressed together between glass plates, so that the blood is expelled from the living tissue, the paper will be promptly blackened in less than 20 seconds' exposure. This is an experiment so convincing that it justifies all the efforts made to render parts anemic. Hence the various compressors and pieces of apparatus which are used for this purpose. Only inasmuch as it is known that ordinary glass itself filters out a large proportion of ultra-violet rays, it becomes necessary in order to obtain the best effects to use compressors made either of ice, rock salt or quartz, since these easily permit the ultra-violet rays to pass through them. The instruments used now should all be provided with quartz plates and adapted to this purpose; hence the expense attached to such apparatus. It is desirable also that the patient be so exposed that the light shall fall perpendicularly upon the affected surface. Working thus with rock crystal and with an electric lamp of 80 amperes Finsen claims to have destroyed the micrococcus prodigiosus in one minute, and to have practically disposed of lupus nodules, so that they would shrink up and disappear after fifteen minutes' exposure.

This matter of the total exclusion of glass and substitution of quartz or rock salt is more important than has been generally appreciated. The violet rays easily pass through glass but the ultra-violet rays are almost completely excluded by it. Again the difference between the effects produced by the ultra-red and ultra-violet rays should be emphasized. The former, the heat rays, produce more or

less redness of the skin which quickly disappears. On the other hand, the actinic rays produce scarcely any reddening, while their maximum effect is not attained for from twelve to twenty-four hours.

Practically we have to produce the ultra-violet rays either by using sunlight, which limits the production, or by one of two artificial means: the utilization of the arc light or by electric sparks from a condenser. There will always be a certain disadvantage attaching to sunlight, namely, the amount of heat radiation, which must always be prevented by some filtering arrangement, and while copper sulphate solution, e. g., will answer this purpose, it also takes out some of the other rays which one does not want to lose.

If an arc light could be provided with iron electrodes a much larger number of ultra-violet rays would be given off than are produced by carbon, but then the arc light so made would be a source of a large amount of radiant heat. Electric sparks are known to give off light of high actinic value, and so-called condenser spark lamps have been devised, and are now on the market, by which a discharge is made to pass between two electrodes, which preferably are of iron. Such lamps are useless, however, unless they are provided with quartz fronts or lenses.

The salts which ordinarily fluoresce are not so sensitive to the ultra-violet rays as to the Roentgen rays, and the fluoroscope cannot be used with the Finsen light.

The ultra-violet rays have this most peculiar property, that they can discharge a negatively electrified body, in which respect, of course, they differ from the condenser sparks, which will discharge any charged body, from which it is evident that the condenser spark is very much richer in these rays than the arc light. They can also produce nuclei for cloud condensation in moist air, and finally, in addition to this, they have a special action on the skin, at least of the higher animals, and on the entire tissues of the lower animals and plants which has been already noted.

When tested carefully as to its transparency to the ultra-violet rays a sheet of glass one twenty-fifth of an inch thick proves to be as opaque as a piece of hard rubber one-fourth of an inch thick or as the entire hand. The most transparent material is polished

pure rock salt which must, however, be kept both clean and dry in order that it may preserve its properties.* A condenser spark lamp has also this advantage, that it does not radiate heat and that only a simple cooling arrangement is required, and that while rock salt forms the best compressor a piece of ice may be advantageously used, since the anemia produced by this pressure is increased by its coldness and its opacity to radiant heat.

SUMMARY.

We thus have two therapeutic agencies affording us methods of treatment which are so new and to such an extent still on trial that we must hesitate lest enthusiasm run away with judgment in discussing their merits and their applicability.

Nevertheless the results of extensive experience may at least be formulated in the following safe and warranted conclusions:

1. They afford methods of treatment for extremely new growths of limited area and superficial character, which, while not exactly certain, are extremely promising.

2. They not only cause no pain but tend to relieve pain, both superficial and deep, in a most pleasing and satisfactory way.

3. They are adapted to cases which can hardly be submitted to any other method of treatment, and they afford more hope in delayed or inoperable cases than does any other method of treatment.

4. It will be found that the odor of putrefaction may often be suppressed by their use and the putrefactic process itself checked.

5. Burns and intense dermatitis, so frequently noted when the treatment first came into vogue, may now be almost certainly avoided.

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*At the meeting of the American Physical Society in Dec., 1902, Prof. R. W. Wood described and exhibited a screen which was transparent to ultra-violet light, while being opaque to the rest of the spectrum. Such a screen is very useful in photographing ultra-violet spectra, since it enables the overlapping spectra of other orders to be eliminated. The author showed an interesting lecture experiment in which the rays of the lantern, after passing through such a screen, were concentrated to an invisible focus, where a suitable fluorescent substance was excited. The screen was made by combining a gelatine film containing nitroso-dimethyl-aniline with copper oxide and cobalt glass.—*Science*, Jan. 30, 1903, p. 182.

6. More than this, they afford a supplementary method of treatment after operation, by which the benefits of the same may be enhanced and enlarged.

7. It is not necessary to intermit such work as the patient may be engaged in in order to carry out the X-ray or photo-therapeutic method of treatment.

Of course it is not fair to expect too much of such agents, especially of those so new. One of the most comforting aspects of their use is the relief from pain which they afford, even when this pain is deep-seated and of uncertain origin. Even such use of the X-rays as is called for in an ordinary fluoroscopic examination, has been known to relieve pain, although by it nothing else was accomplished.

What it may accomplish in deep cases is as yet pure conjecture. Without entering into detailed reports I am at least positive of this, that in certain inoperable cases of intra-peritoneal cancer and tuberculosis, accompanied by more or less ascites, kathode rays have certainly relieved pain, retarded extension of the disease and apparently been of great benefit, even if such benefit prove but temporary. This of itself is of greatest value, and can be accomplished better in this way, perhaps after an abdominal section, than by any other measure with which I am acquainted.

The X-rays apparently will also relieve itching in certain instances, and may especially be used for removal of hair, for cosmetic reasons or in treatment of sycosis, of favus, of psoriasis, and will be found serviceable in the removal of those birthmarks which are covered with, or surrounded by, considerable growth of hair. So far as photo-therapy is concerned, it must necessarily find its widest range of application when the disease is limited to a small area and is superficial. Morris and Dore have shown (British Medical Journal, February 9, 1901, p. 326) that there are certain skin conditions which are not favorable for photo-therapy, especially such scarring as results from previous scraping, pigmentation by which the ultra-violet rays are intercepted, vascularity in those parts where a compressor of some kind cannot be applied, deep lesions, and those of skin or mucous membrane whose location makes it difficult of treatment, e. g., about the eye, in the nose, mouth, etc.

February 1, 1903.

AN EPITOME OF THE HISTORY OF CARCINOMA.

By Roswell Park, M. D., LL. D.

No one can scan the voluminous literature of cancer without being at first bewildered by the confusion of names and the loose and almost meaningless way in which the term and its various synonyms have been used. It is bad enough even to-day when one writer describes a growth as cylindroma and another writer rejects the term. If this be bad to-day when we have reasonably accurate notions of what constitutes cancer, how much worse must it have been centuries ago when a hundred different conditions were described under the same general term. It does not seem worth while to go back to the beginning of the Christian era since the writers who followed Hippocrates simply represented his views, and we do not need to trace them into antiquity. Let us then begin with Celsus, who wrote "carcinoma" in its Latin spelling and did not use the Greek "karkinoma," although many of his translators have done so.

In his day, and long after, ulcers of all kinds were confused with tumors of all kinds, which will account for his making particular mention of venous stasis and swelling veins, and noting the fact that sometimes carcinoma causes pain and breaks down into an ulcer and at other times not. He took this view—that if the actual cautery produces no bad effect the disease is curable, whereas if the growth is stimulated by the cautery it is a carcinoma and active therapeutics must be discontinued. It is a curious fact that the theory of the development of cancer given by Celsus should be made the basis of an essay by Schmalz in 1825 *(Surgical Treatment and Surgical Diagnosis)*.

The early writer and his late imitator distinguish some sixty or more different kinds of ulcers, among them those due to a peculiar

diathesis, *i. e.,* cancerous, and so he described ulcus cancrosum, cancer apertus, cancer genuinus, noli me tangere, open cancer, glandular cancer, etc. Celsus used frequently the term cacoethes in the substantive sense, whereas Schmalz uses it as an adjective, *i. e.*, cancer-like. In his clinical descriptions Celsus was painstaking and often accurate. In fact he used adjectives very freely. Chironium and telephium were terms applied to an ulcer accompanied by severe pain, induration and general formidable appearance with tendency to spread. Such terms might apply equally well to a malignant ulcer or a chancroidal bubo.

According to the Celsian view, should the suspected ulcer not improve under appropriate treatment it is certainly a cancer, but no one could make the decision without time and experiment. Writing of this, Thiersch quoted the *bon not* of Duparque to the effect that " Cancer is incurable because it cannot be cured; the reason we cannot cure it is because it is incurable; therefore if one by chance should happen to cure it, it must be that there was no cancer." They had in those days also what was called *thymium,* a lesion of doubtful character, about which there was much uncertainty. Celsus remarks that " it is like a wart, and therefore in some respects must be different but occasionaly is found on the surface of an ulcerating cancer. Nevertheless it has an independent growth of its own."

This would look like the so-called " proud flesh " of the laity as the expression, " then comes the ulcer and from it the thymium," would imply. This word, by the way, is spelled also tymium and timium. The expression seemed to the writers who used it very apt, although the younger Pliny used it in the sense of a simple swelling, and applied it indiscriminately to a boil, a pile, or a condyloma. The thymium was not very different from what was called *akrochordon,* which was described as species of wart, sometimes very painful, ovoid in shape, connected to the skin by a slender stem and known as the " hanging wart." It was so-called because the cutaneous surface resembled the cut end (*ἄκρα*) of a harp string (*χορςή*). According to some descriptions the former would appear to be a simple horny outgrowth from the skin, and the latter a fungous

papilloma; according to others, who use the expression *pessimae,* we are compelled to regard them as something more serious. In addition to the terms now strange to us, above mentioned, Celsus also used the words *murmakia* and *clavus,* which latter is still in use. Clavus in his day seems to have signified a pus-producing swelling.

Celsus seems to have been conversant with the step by step process of infection, both malignant and pyogenic, but I think that we waste time in trying to determine more minutely just what he in his day meant by these terms which I have thus far rehearsed. So late as 1777 Blancardus contented himself with presenting this subject practically in the language of Celsus, adding nothing thereto, and having in his preface scarcely a word to say for himself on the subject; but the more one examines Blancardus the more evident it is that he was destitute of enterprise in medical research. There is no question that Celsus lived at a time when men had no use for the exact sciences, as even the elder Pliny acknowledged. The world was given over to excess and debauchery, and the worst form of imperialism controlled Roman thought. Medical literature of that date consisted mainly of formulæ for cosmetics, and while the baths were conducive to health and to cultivation of artistic taste, they were destructive to public morality. Some effect was produced by the alarm voiced by Plutarch and Tacitus, by the merciless satires of Juvenal and Perseus, and by the well directed philosophy of Seneca.

In the year 131 Galen was born at Pergamos, and he finally appeared in Rome as the private surgeon and medical adviser of the young Commodus. He curiously mingled philosophy and medicine, and combined with the humoral pathology of Hippocrates a pneumodynamic theory mainly his own. To him the malignant character of cancer was well known, and he added to the views of his day concerning its internal manifestations. "In the breasts we often find a tumor in size and shape closely resembling the animal known as the crab, for as in the latter the limbs protrude from either side, so in the tumor the swollen veins radiate from its edges and give a perfect picture of the crab." Here will be seen perhaps the first publicly stated reason for giving to this disease this partic-

ular name. He also busied himself with its treatment, and while he considered cancer to be the product of black bile, was not opposed to operation but gave this advice: first tó get rid of the black bile by appropriate remedies and then to attempt a cure by milder applications since "the more severe remedies merely increase the evil." He told us that there are many metallic compounds which, taken with purgatives, have a beneficial effect upon the disease in its early stages, concluding that if one is "minded to try the cure of cancer by surgery he must as before begin by purging the evil humor, and then immediately proceed to the removal of the diseased part so thoroughly that there shall be nothing of it left, by letting the blood flow freely and being in no haste to check it, but rather squeezing out the thick black blood from the swollen veins." Galen thus showed that he recognized that cancer possessed a malignancy peculiarly its own, for which reason he advocated the combination of medicine and surgery.

Galen operated for cancer with the knife and cauterized the wounds, not alone for hemostatic purposes but for the destruction of any remaining diseased tissue. He noticed that successful results occurred when the operation was carried out, and his language as well as his actions show that he was familiar with true carcinoma, although he was not aware of the function of the lymphatics. He nevertheless was earnest in calling attention to what he knew of metastasis, even through the venous circulation. Evidently with him also it was not only the amount of the humor but its character which determines the subsequent growth, but he says it is the thinnest of these humors which give rise to the herpetic ulcer while the thicker causes cancer. Galen's general pathology was a sort of organic theory of disease. He maintained, in opposition to Archigenes, that it is always by reason of disordered function that a part becomes diseased, and that an organ can only become directly diseased as a result of transmission from other diseased foci. Hence we can readily understand his object in always preceding an operation for cancer by a system of general treatment. If therefore he became enthusiastic in his praise of phlebotomy, or his use of purgatives, we must give him credit at least for some sort of rational basis for his therapeutics.

Following the death of Galen medicine entered upon a period of quiescence if not somnolence. Leonidas of Alexandria, some 200 years after Christ, wrote as follows, if we may trust Aëtius: "If therefore the breast be entirely involved in the scirrhotic growth so that the surrounding part is endangered should an amputation be attempted, under no circumstances should we operate. If, however, the apex or only one-half of the breast be included in the growth, the breast should be removed and the wound cauterized." When he feared hemorrhage he often operated in two sessions, for he says: "I then cut a second time and dissect out the whole breast and afterwards cauterize the wound, often repeating the cautery." The first cautery was for hemostasis, the second for the extirpation of infected tissue.

For several centuries nothing of interest transpired until we come to the writings of Alexander of Tralles, who excelled rather in treatment than in diagnosis. In his ninth book he discusses cancer and offers several methods of treating it from a humoral point of view. Among other things he highly praises the treatment of cancer of the liver by the use of chalybeate waters.

The work of Paul of Ægina is mainly a compilation, in the fourth book of which he treats of external diseases, among them cancerous tumors, for the treatment of which he repeats Galen's precepts; particularly the advice that all operations are to be preceded by free purgation of the black bile. After Paul there came little of any value. Nonus and Mercurius in the tenth century were absolute compilers, and Myrepsos, another of the same class, was dubbed by his contemporaries "the perfumer," polypharmacy being his strong point. His book on medicine is an alphabetic breviary, divided into 48 chapters, containing some 300 senseless prescriptions with pathetic appeals to God and Christ. His treatment of cancer is included under the head of "aromatics and specifics for the cure of lice and spots on the skin."

The Arabs were too firmly bound by the authority of Galen to make any advance. They added still more to the polypharmacy of their day, and not until the time of their later scholars was anything of value said regarding cancer. Avenzoar, however, who was really

of Hebrew origin, showed a rather remarkable knowledge of pathology, as is illustrated in his discussion of cancer of the stomach. Some of their writers advised early extirpation of cancer and of all infected tissue. Albukasim remarks, "When cancer has become old and large you should have nothing to do with it. I have never been able to cure one, nor have I ever seen any one who has."

The notions of the Arabians were reflected in the Latin writings of the middle ages. William of Salicet says "Cancer is a tedious disease—the more you interfere with it the worse it becomes." He frequently termed it *noli me tangere.* Lanfranchi says: "The general rule with cancer is that it can only be cured when it can be entirely removed, along with its roots." He had noticed the occurrence of cancer in badly healed wounds and advised their partial cauterization—for the purpose of diagnosis. If the growth increased it was an original cancer. Guy de Chauliac endeavored to recognize the cause of cancer; his conclusion was: "Ulcerating cancer is caused by the existence of a former non-ulcerating cancer, or the irritation of chronic ulcers." He also held that if it be in a locality where it can be entirely removed it should be operated; if not, no attempt should be made save at palliation. He advised caustics for causing the death of suspicious tissue, and considered arsenious acid as desirable for this purpose. If the diseased tissue was thus completely destroyed the fact was shown later by the advent of a scar and healthy appearance of the adjoining flesh.

But in time all operations fell into disrepute and cancer came to be regarded as practically incurable. The theorists of the middle ages, with their immutable dogmas and superstitious reverence for Galen, obstructed progress in every direction. Cancer was as before, "an ulcer of horrid appearance, evil smelling, and presenting a hard, thick, discharging, everted border."

It was centuries before men could break away from the use of the red-hot knife. The celebrated Fabricius, he of Aquapendente, advised that glands be seized by forceps and cut away with a red-hot knife, or that an incision be made about the breast with a wooden or horn knife previously dipped in aqua fortis, and the glandular substance subsequently removed by the means of the finger and

nails. But let us give the credit due to Fabricius for the suggestion to feed by a tube introduced through the nose into the stomach in cases of œsophageal contraction.

Paré, great man as he was, did not make the advance in this direction which might have been expected of him. He did not even do as well as did Fabricius Hildamus, who achieved the title of a noted operator because he operated with the knife, ligated the vessels, and dissected with his fingers. He also cleaned out the axilla in breast cases and conducted many cases to recovery. Paré was in most respects a follower of Galen. Dyscrasis was the ghost that haunted medical literature for centuries, and is not even yet quite forgotten. "Cancer is from black bile," said Galen. "Cancer is the product of melancholie," falls like an echo from the lips of Paré, who described under the head of melancholic tumors true scirrhus and other cancerous tumors corresponding to the cacœthes of Galen.

Paré distinguished four kinds of tumor due to black bile:

1. The hard schirrus proper, which is accompanied by no pain, is not sensitive on pressure, and is caused by natural black bile.

2. The imperfect, rough, painless, stone-like schirrus, which is caused by great chilling or disintegration of humors.

3. The cancerous schirrus caused by heating and corrupting of the humors.

4. The schirrus phlegmonides, which is caused by the mixing of the bile and the blood.

Paré's treatment for these various conditions included abstinence in all respects, the classic method of black bile purgation and the external use of counterirritants, fumigations, mercurial plasters, goat dung, and many other more savory applications, beyond which ingenuity could scarcely go. Paré described the transition of cancer occultus into cancer apertus, *i. e.*, non-ulcerating into ulcerating forms as clearly as any clinician could desire. The pain, irregularity of shape, tendency to hemorrhage, oozing discharge, infiltration, etc., he faithfully portrayed. On one of his pages he gave a picture of a large sea crab, and says: "Also the cancer is brownish blue in color, and uncouth in shape, like the animal whose picture

is appended." He realized that women are more subject to cancer than men, called attention to the frequency of infiltration and metastasis, did not decry operation, but reminded his readers of the thirty-eighth aphorism of Hippocrates, which counsels against operating upon deep-seated, occult cancers or those of long standing, or those occurring in patients of feeble constitution. He advised the use of sweet milk to destroy the odor of cancerous discharge.

His operative methods comprised two distinct procedures: the excision of the tumor with a broad margin of healthy tissue, with compression of the neighboring vessels and vigorous use of the hot iron, or the elevation of the tumor by means of a thread passed through it, its extirpation by means of scissors, with lateral incisions when necessary for relief of tension.

Throughout the seventeenth century black bile continued to be regarded as the chief cause of cancer. Frere Côme set a good example to posterity when after having purchased a secret nostrum he made public its ingredients, which were about as follows:

Cinnabar	2 parts
Ashes of old burnt shoes.................	3 parts
Dragon's blood and white arsenic, each....	12 parts

This was applied in dry powder or in paste mixed with oil.

One of the earliest real departures made from the old tenets was that of Le Dran, who in 1757 published a work in which he showed the purely local character of cancer in its beginning and then formulated the best methods of cauterization. He devoted considerable space to the discussion of tumors of the breast of which many are curable, and expressed the opinion "that not all is cancer which has been taken for such." Soon after this came Louis's publication on fungous growths of the dura and diseases of the eyeball, including cancer of the eye. Still confusion of terms complicated everything, and in Plenk's essay on skin diseases, published in 1776, he described 18 sorts of tumors, including inflammatory tumors, pus tumors, gangrenous tumors, hard tumors, water tumors, blood tumors, etc. This reminds me very much of the hospital that I

visited in Seville a few years ago, where one ward was reserved for "Dolores," all patients who were suffering pain being sent there.

Richter describes two classes of tumors: Inflammatory and non-inflammatory, placing cancer among the latter. His remarks are quite in accord with those of van Swieten, who describes them as bad smelling, easily bleeding, rodent, ulcerating growths, which are found on the lips, tongue and genitals. Schirrus they described as a hard, painful tumor situated in an organ rich in glands and having a tendency to cancerous growths, and then admit that these growths may arise from cracks, excoriations, styes, etc. Even Richter could not get away from the old black bile, but he held that it could not arise from inflammation alone. He regarded dyscrasiæ as predisposing elements in causation of cancer. Together with his colleague Schmucker, he denounced bitterly the use of corsets as the invention of "that accursed Pompadour."

While Hunter's contemporaries were playing with belladonna and rabbit skins and all sorts of quackery, Hunter himself was experimenting with the control of fixed tumors by means of compression, but by fixed tumors he meant inflammatory lesions whose nourishment he was trying to reduce by pressure. Fischer and Desault were trying to accomplish the same thing in the case of rectal cancer by the use of rectal bougies. The writings of Munro threw operative treatment into such disrepute that the Amsterdam Guild of Physicians felt called upon to offer a prize of 100 ducats for a safe and practical method of curing cancer. As may be imagined, numerous remedies were proposed, and now came into repute the wonderful properties of cicuta (water hemlock or cowbane) which ran about the same course in those days that cundurango did in ours. As the result of disappointment with all these remedies, operative methods came back again into vogue. Cancer of the breast, lip and scrotum were generally operated upon. Finally Petit gave formal expression to insistence upon the necessity for the removal of swollen glands of the axilla in cases of cancer of the breast.

And next came the French Revolution, which not only shook the nation to its very foundations, but was a new era in that the authority of the ancients was no longer revered. A cold materialism sought

to derive everything from the inherent properties of matter. Mysteries were no longer tolerated. The doctors of Paris even went down to the halls of death and sought to find the seat and secret of life among the still bleeding heads of those who had been guillotined. It was in 1773 that Peyrilhe declared that to cure cancer, even to define it, was extremely difficult, which bit of wisdom won for him the Dijon prize. Morgagni died in 1771; just thirty years later Bichat gave the final touches to his great work on anatomy. During the winter of 1801 he himself made 600 autopsies in the Hôtel Dieu. Of his work Corvisart wrote to Napoleon that no one in so short a time had done so many things and done them so well. He was the first to distinguish between stroma and parenchyma in tumor tissues, although he ascribed a fallacious importance to connective tissue.

Bichat's spirit survived, although he died a most untimely death, for Laennec made a sharp distinction between carcinoma together with tubercle, and melanotic and other growths, basing this upon their histological structure. Some of the writers of that day saw about these cases that which they regarded as infection, and endeavored to trace its path in the blood vessels and thoracic duct. In the same way we owe to Laennec our insight into the relation of cancer to the internal organs. He also pointed out that schirrus is not merely a hard tumor and a forerunner of cancer, but of itself a distinct form of connective tissue cancer, which he classed along with the encephaloid, melanoma and tubercle being placed among heterologous growths.

It was perhaps Lobstein who first divided tumors into the homologous and heterologous or heteroplastic. He held that those of the latter form arise from some form of lymph that has been introduced into an organ from an outside source. This lymph was compared by Lobstein to Hunter's wound and infiltration lymph, agrees entirely with the blastema and exudate of Rokitansky and even later authors, and is either benign or malign, the latter giving rise to cancer. By the efforts of the school to which Lobstein belonged, including such men as Andral and Cruveilhier, Billard and Velpeau, the differential diagnosis of tumors of the breast was greatly advanced, while such men as Astley Cooper in England and Walther in Germany were quite won over to these views.

After this the French rather retired from their advanced position, and their place came to be occupied more by German investigators. Stieglitz, writing in 1840, made this sad confession concerning his German colleagues: "German medicine is so far degraded and spiritless that any stimulus whatsoever that pushes it forward in a new road is sure to be of benefit, even though the path be beset with errors and perversities." Soon after this, however, all Germany began to move forward and scores of names are inscribed in imperishable characters in its history of medicine for the past half century. The theory of cancer profited by this forward motion and soon appeared in new dress. In the beginning of the third decade microscopical diagnosis was still a *pium desiderium.* Johannes Müller, after years of work, described six kinds of operable tumors and seven kinds of carcinoma, which could not be cured by extirpation. Our knowledge was materially advanced by the researches of Schleiden and Schwann into animal and vegetable cells, by which many other things were to be reconciled. The allusions of Müller, in his third edition (1838), to the more delicate structures of pathological growths called forth numerous contributions of a similar character from other writers. Moreover, he held that cancer formations do not arise from primitive tissue by degeneration but are produced by new cell formation, deposited as a specific element of disease in the normal connective tissue of the organ. He found also in this statement an explanation for the general infection certain later to pervade the whole system. Translated into the thought of to-day, the most advanced of us would scarcely go beyond a similar doctrine. Müller is believed to have been the first to demonstrate the presence of nucleated epithelium in cancer. Naturally, with such views, Müller discarded all distinction between homologous and heterologous growths. This was taken up by Henle in 1839 and by Vogel in 1842, and an effort was made to prove that each growth is really a variation from normal growth due to defective or to active individual mother cells. About this time also began the attempt to discover specific cancer cells, with the microscope, whose significance would be of greatest importance in diagnosis. This effort was car-

ried altogether too far, since some enthusiasts denied the accuracy of all diagnoses where such cells were not found.

In 1847 great mischief was wrought by the introduction of the term cancroid by Bennet. This was to be the term by which all growths were to be known where the specific cancer cell could not be found. Then Virchow and Förster, as well as Lebert in 1850, limited the term chancroid to diseased tissue which presented alveoli with epithelial collections. Therewith epithelial cancer became the cancer par excellence, and many tumors took the name of sarcoma which hitherto were considered carcinoma. In 1852 Hanover introduced the term epithelioma, and Robin and Bidder described cylinder epithelium cancer. By this time confusion in terminology was almost complete, and now for several years the epithelial cell, in epithelial cancer, was regarded as arising independently of pre-existing epithelium from connective tissue corpuscles. It was apparently von Bruns who in 1847 first emphasized the role of the lymphatics in spreading this disease. Even in 1856 the condition was still regarded as uncertain and was the cause of many controversies.

J. Müller had already reported upon the spores given off by the body humors in cases of carcinoma, and it had been frequently noticed that in cases of melanotic cancer these were heavily charged with pigment. It was not long now before pathologists were divided as between those who held that primary cancer becomes constitutional by a general infection through the blood vessels, by means of a blastema or virus of some sort (theory of infection) and those who regarded the constitutional effects as due to the transmission of epithelial constituents and debris (theory of transplantation). Others yet saw in primary carcinoma only a local expression of a general carcinosis already acquired. The rest of the history of cancer is certainly well known, and it is scarcely necessary to attempt to bring it down beyond the pioneer experiments of Waldeyer and Volkmann's early researches. It was through these studies that some sort of order was finally restored, and that ideas which presented an indescribable jumble were more or less simplified.

SPECTROSCOPIC ANALYSIS OF THIRTY-SIX VARIETIES OF CONTINENTAL AND AMERICAN ORTHOCHROMATIC DRY PLATES.

BY F. S. LOW, ASSISTANT IN PHOTO-CHEMISTRY.

The multiplicity of uses to which orthochromatic plates are put has of late years so increased the number of brands on the market that scarcely a dry plate maker exists who does not offer one or more varieties of this product to the purchasing public. From this greatly increased demand and production certain improvements and a greatly increased variety of plates have resulted, and there are at least some makers whose products present a high degree of uniformity. The greatest advance has been in the keeping quality of the plates. Every operator who has employed color sensitive plates under exact conditions, such as in microphotography and three-color reproduction, has, however, learned, in most cases to his sorrow, that the plates have seldom fulfilled the claims of the makers.

The claims made for plates are usually of a very general character, ranging from the statement that they are "highly orthochromatic" to specific data in the case of a very few. The disadvantages of this state of affairs are naturally great. In the photographic work of this Laboratory, which includes more or less all the photographic processes, we have found it absolutely necessary to analyze the different brands in use. As a result we have been able to select plates best adapted to the subject in hand. For this purpose we use a simple diffraction spectroscope fitted with a replica of a Rowland grating. These replicas can now be had at a small cost, and every dry plate manufacturer, as well as every scientific photographer, can afford to possess such an instrument. With such a spectroscope the testing of the plates is a simple matter. The spectrum obtained by the grating is projected upon the plate by a photographic objective,

and the dark slide is so arranged as to permit a series of exposures on one plate. The time of these exposures, the illumination (sunlight at a certain elevation) and the length of development with a standard developer being determined, it is possible to chart the distribution of the sensibility of the plate.

As, on the whole, more reputedly good orthochromatic plates are to be had on the continent, especially from German and French makers, we purchased in the open market two packages from each maker and tested plates from each package. With the continental plates we have also tested the leading American brands. There remain yet certain English brands which deserve attention, and these we hope, for the sake of completeness to add to those here published. As the results obtained are not only of interest but have proven of great use to us, we have decided to publish the thirty-six varieties so far tested. All exposures have been made with a wedge-shaped slit which enables us to construct a curve representing the relative sensibility of the plates. In the diagrams the relative speeds of the various plates are represented by vertical values in the curves, while their color sensitiveness is represented in horizontal values. Sunlight has been employed as the normal standard, the different Fraunhofer lines enabling us to determine with ease the distribution. In each case we give an underexposed and a normally exposed spectrum. It will be seen that the distribution and in many cases the sensibility of the plate in underexposed negatives shows great defects. For instance, in brands No. 5, 11, 15, 25, 26, 27, 28, 29, 32 and 34 there is a distinct break in the continuity of the spectra, usually in the neighborhood of the E line. In many of these brands this defect is more or less repaired in the fully exposed plates. In using these plates it is therefore imperative that the negatives be fully exposed. In underexposed negatives from these varieties strengthening will not repair but increase the defect, as the plate in the region of the E line has not been affected by the light in question.

The relation between the yellow-green sensibility and the blue sensibility is in orthochromatic photography very important. Many

of the plates show extreme blue sensibility and very low yellow-green. The poorest showings in this regard are Nos. 4, 5, 8, 9, 17 and 24. These varieties would require a very dense yellow or orange screen, and when properly corrected would prove very slow. A number of varieties will be found in which the yellow-green sensibility is equal or nearly equal to the blue. A yellow screen to reduce the blue would render these plates orthochromatic.

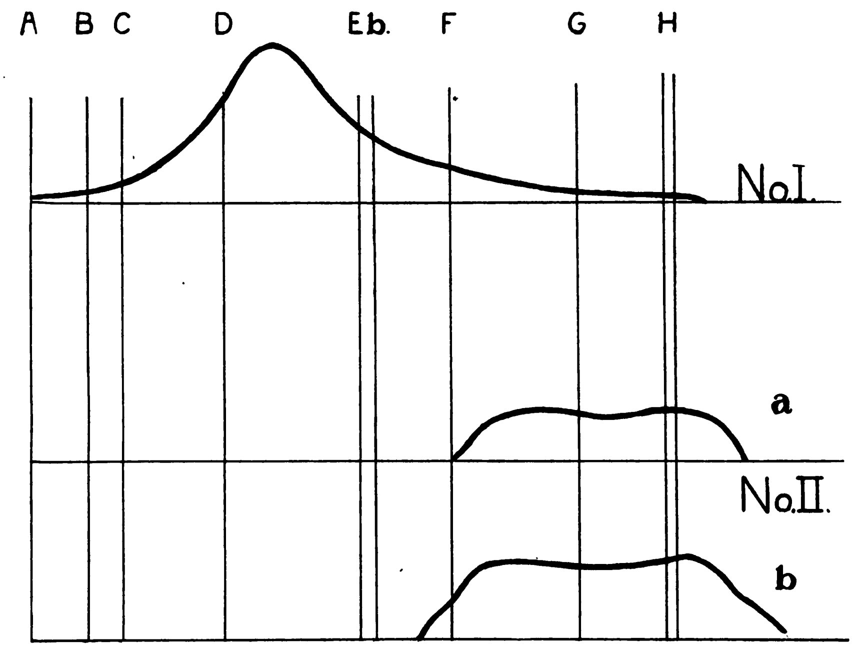
It is perhaps well to recall the order of relative luminosity which the colors of the spectrum present to the human eye. The most brilliant are orange, yellow and green, the least red and blue. The relative brilliance of the colors is shown by the accompanying curve (Fig. I). The plate which most nearly represents this curve and which has a much greater yellow sensibility is No. 29. This plate can, as the manufacturers claim, be used with success without a correcting screen. A very pale yellow screen would render the curve more exact. A number of other varieties will be found in which a comparatively pale screen will accomplish the same purpose. The varieties which show red sensibility are 15 and 28, while No. 29 shows marked orange sensibility. In No. 15 the blue sensibility is greater than the red and yellow, while a wide area of relative insensibility extends over the green. No. 28, on the other hand, shows a practically continuous spectrum with a slight depression between the red, orange and green, and between the green and blue. Both of these plates can be used for three-color photography, No. 28 for all three exposures, and No. 15 for the red and blue, with a green-sensitive plate for the green exposure, such as 23 or 33. No. 28, the Perchromo plate of Perutz which is manufactured after the receipt of Miethe and Traube, is said by these authors to give the relative sensibility of the three exposures, as, 1 for the red, $\frac{1}{2}$ for the green, 1 for the blue. Allowing for the density of the different screens it would appear from the spectrogram that these figures are correct. The general sensibility of the plate is, however, not great. A surprising green sensibility is shown in No. 36, the only film tested. This variety would require a deep yellow screen to correct the blue sensibility.

The appended curves are plotted from what we considered to be a normal exposure. It is somewhat hard to say how much farther into the red the curves could be made to extend by longer exposure, as the portion of the plate covered by the spectrum gradually becomes affected by reflected light as the exposure is lengthened, making it difficult to determine with exactness just how much of the action is due to direct light and how much to reflected.

I wish to express my thanks to Dr. Gaylord for suggestions leading up to and during the course of this work.

I. Fraunhofer luminosity curve.
II. Ordinary gelatine bromide plate.
1. Dr. Smith's Swiss plates.
2. Hauff orthochromatic, extra sensitive.
3. Hauff orthochromatic, isolar.
4. Bremer orthochromatic.
5. Bremer isolar and orthochromatic.
6. Steinschneider's erythrosin orthochromatic.
7. Sandell color sensitive, isolar.
8. Sacs plain orthochromatic.
9. Sacs plain orthochromatic, isolar.
10. A. G. F. A. plain orthochromatic.
11. A. G. F. A. orthochromatic, isolar.
12. Kuzka plain orthochromatic.
13. Mather permanent orthochromatic.
14. Lumiere A green sensitive.
15. Lumiere B red sensitive.
16. Talbot orthochromatic.
17. Lomberg plain (non orthochromatic).
18. Badische erythrosin.
19. Apollo plain orthochromatic.
20. Weisendorph and Weimer plain orthochromatic.
21. Weisendorph yellow sensitive erythrosin.
22. Dr. Schleussner's plain orthochromatic.
23. Dr. Schleussner's "Viridin," yellow green.
24. Herzog plain orthochromatic.

25. Schippang's F erythrosin silver process plates, color sensitive.
26. Schippang's B erythrosin silver.
27. Schippang's B erythrosin.
28. Perutz perchromo.
29. Perutz perxanto.
30. Perutz perorto.
31. Perutz eosin silver.
32. Seed's orthochromatic.
33. Cramer's orthochromatic.
34. Forbes orthochromatic.
35. Eastman's " Kodoid " orthochromatic film.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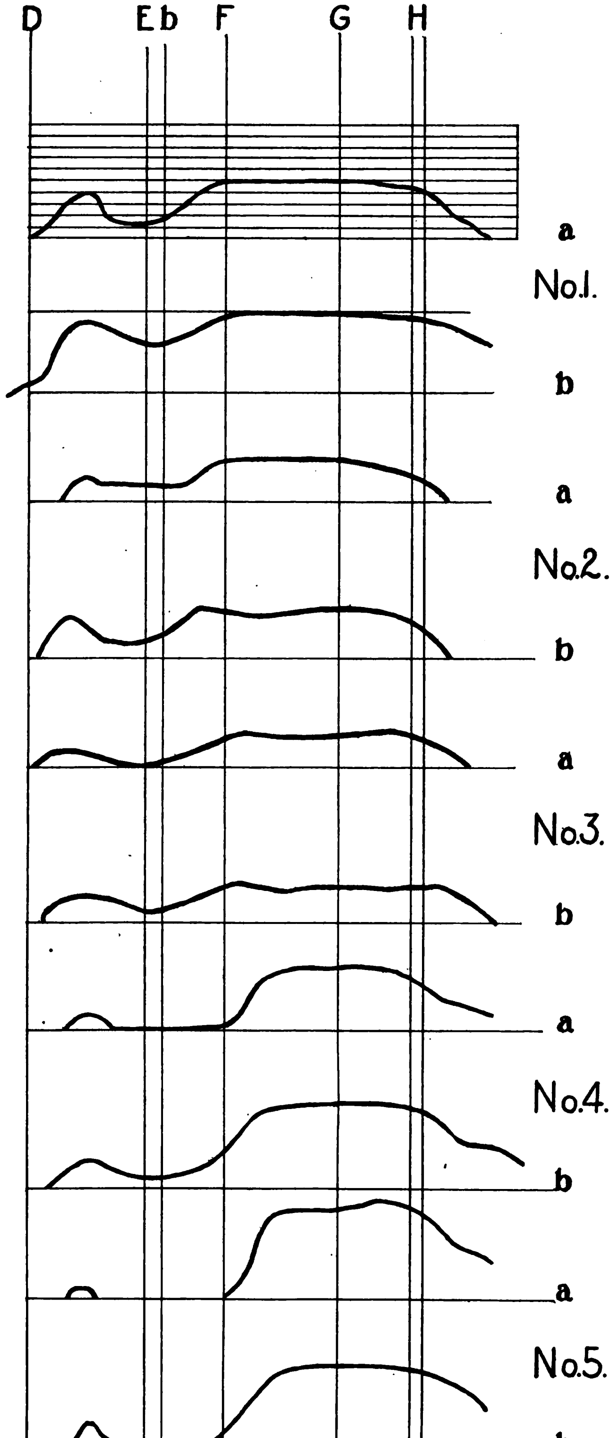
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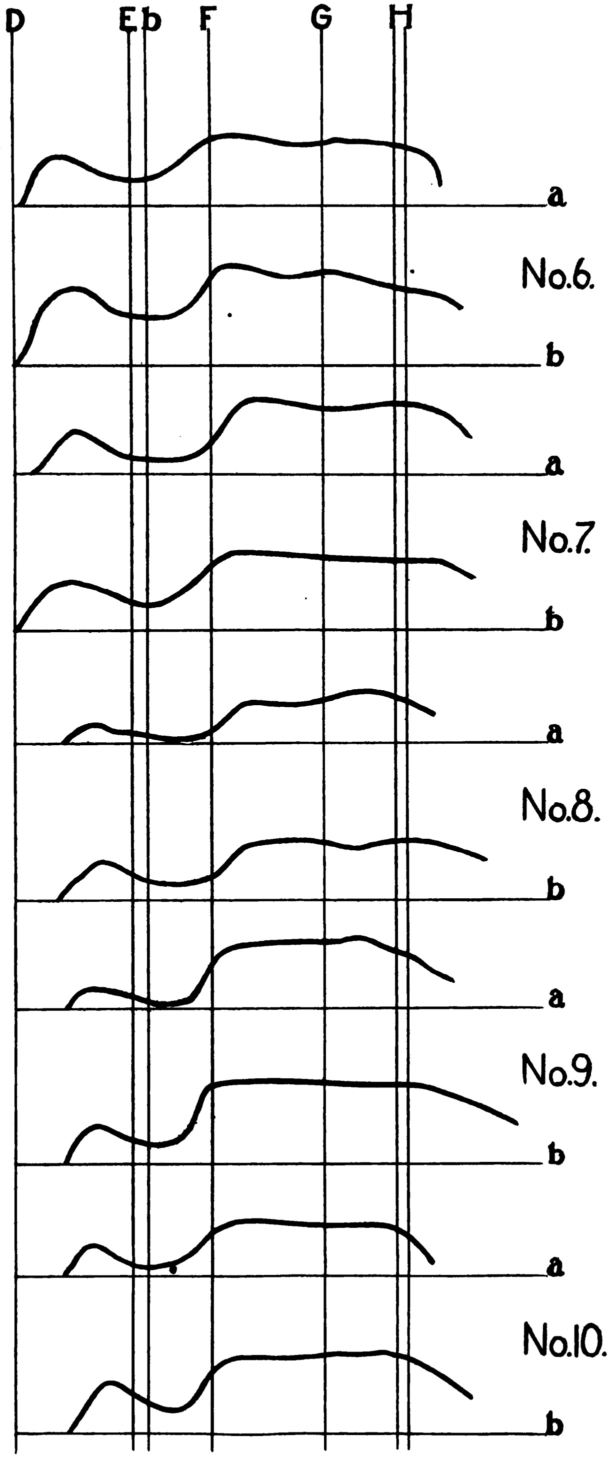

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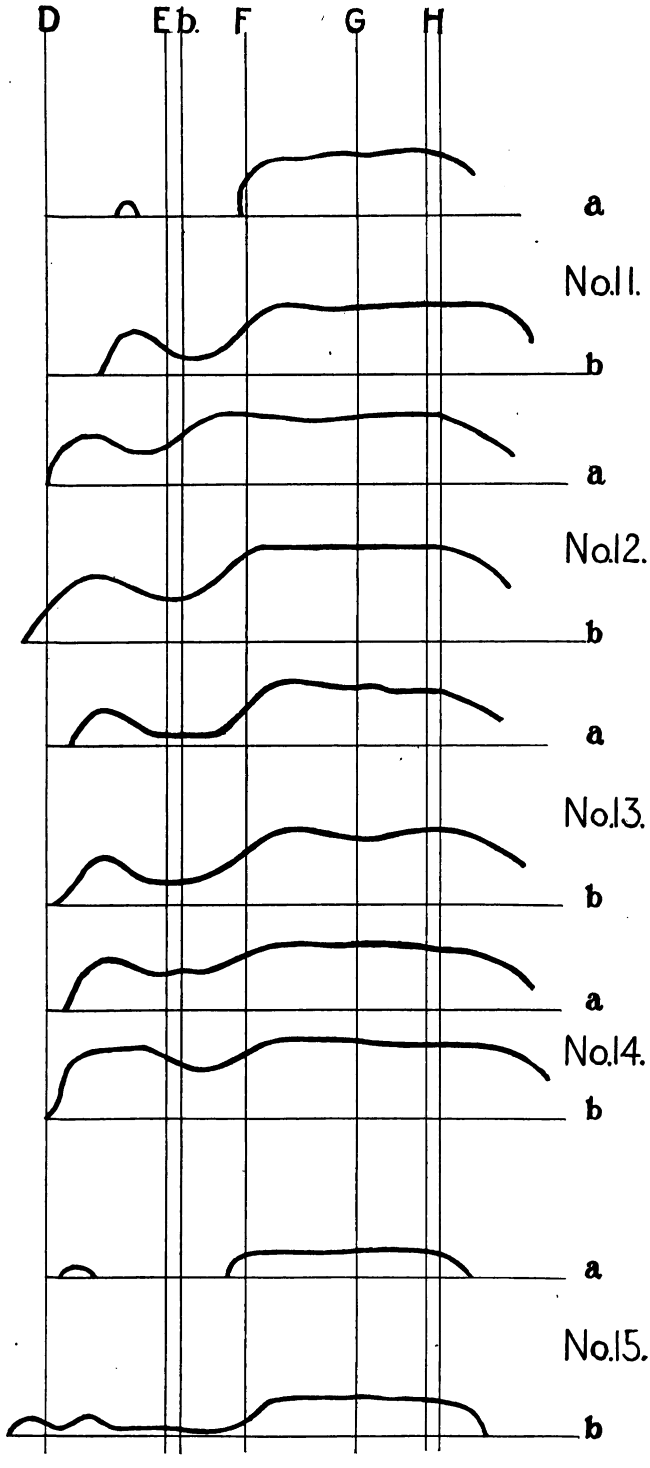

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No.13.
b
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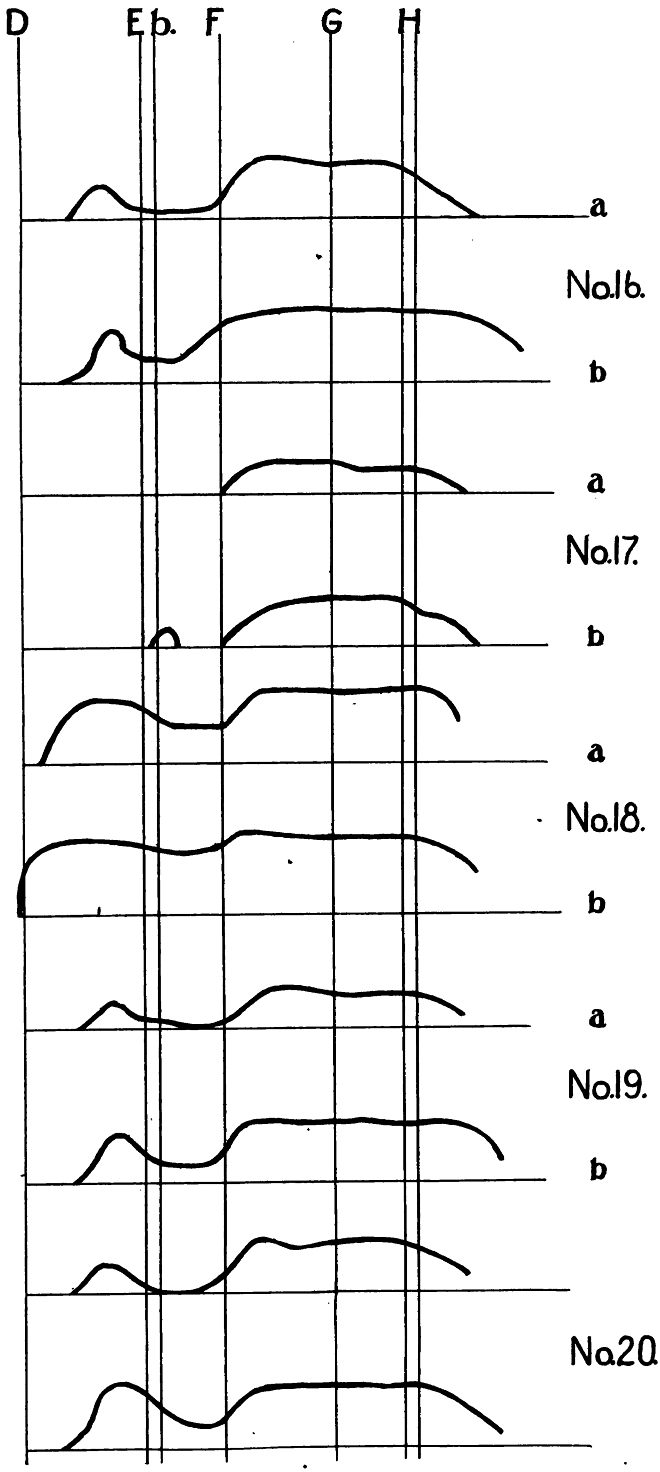
No.14.
b
a
No.15.
b


D
E
b.
F
G
H
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b
a
No.17.
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No.18.
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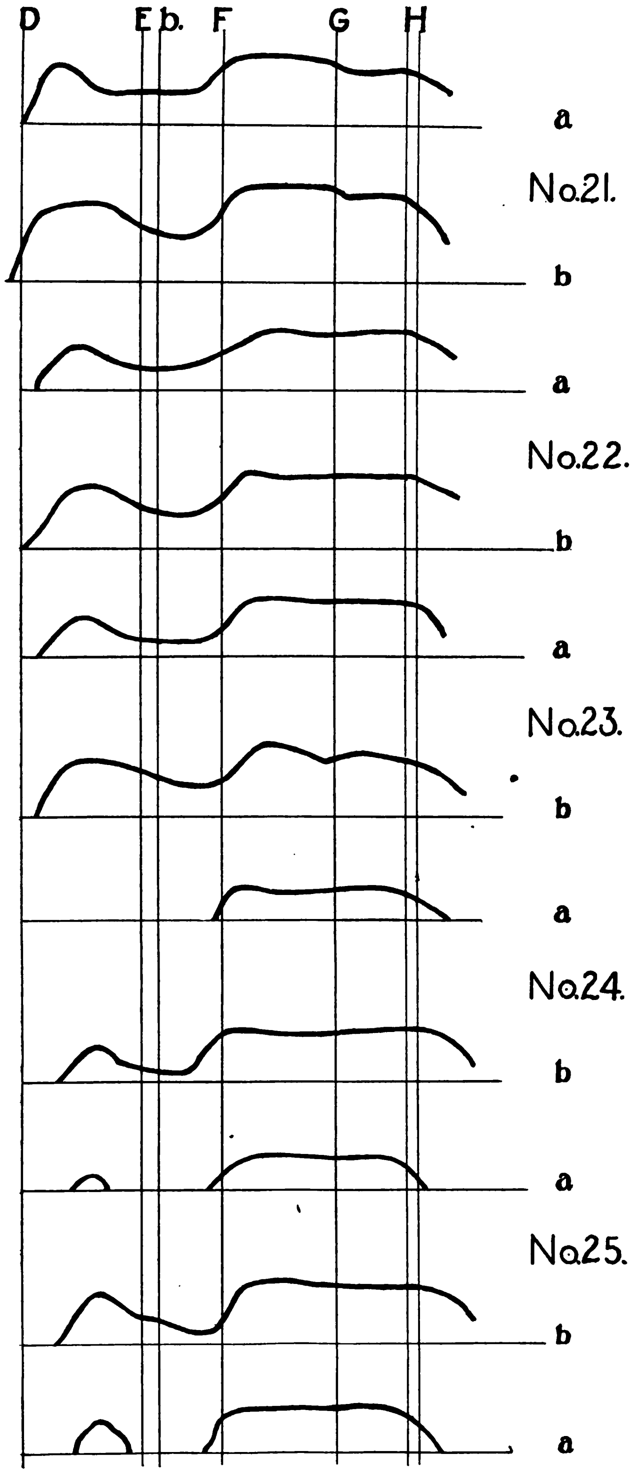
No.19.
b
No.20.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F
G
H
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No.22.
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No.23.
b
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No.24.
b
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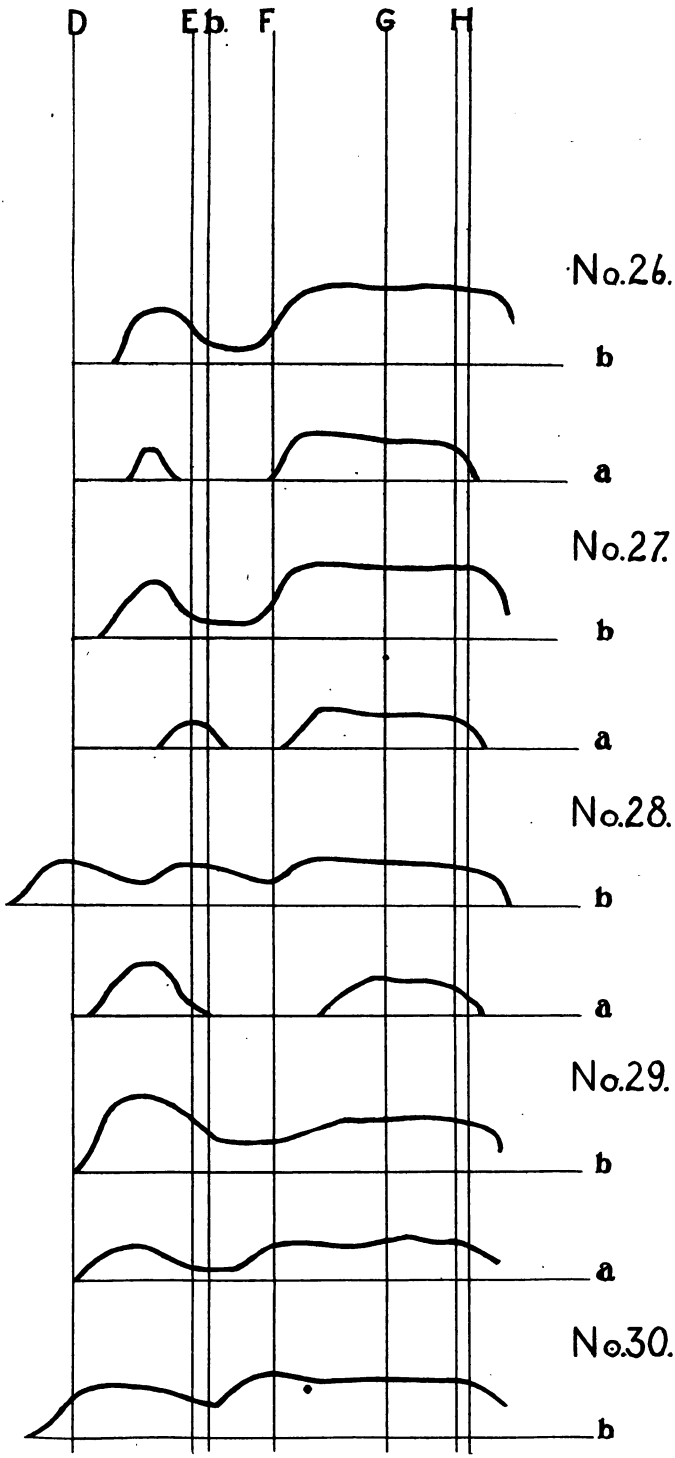
No.25.
b
a


D
E b.
F
G
H
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No.27.
b
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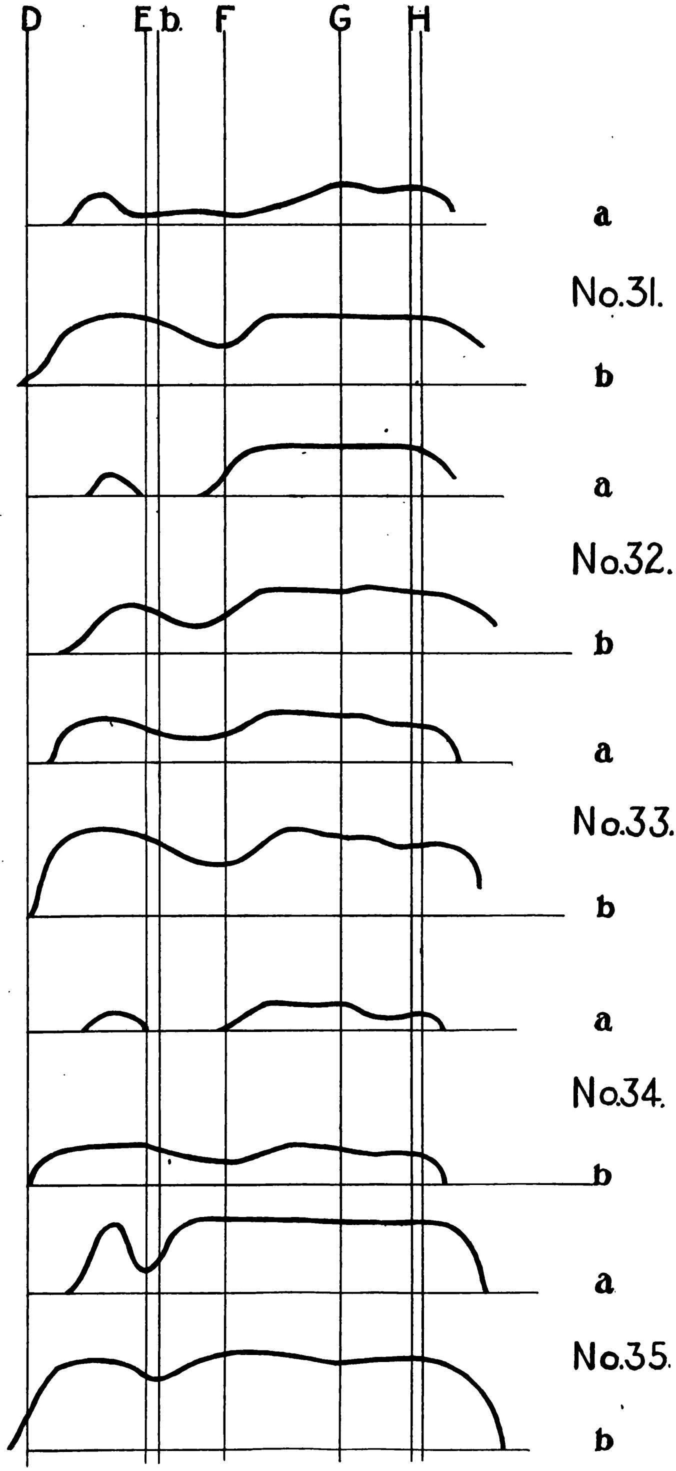
No.28.
b
a
No.29.
b
a
No.30.
b


D
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b.
F
G
H
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b
a
No.32.
b
a
No.33.
b
a
No.34.
b
a
No.35.
b